

ANNALS OF INTERNAL MEDICINE

MAURICE C. PINCOFFS

Editor

VOLUME 16

(OLD SERIES, VOLUME XXI)

January to June, 1942

Contents

NUMBER 1, JANUARY, 1942

Antibody Response of Patients with Pneumococcic Pneumonia Treated with Sulfadiazine and Sulfathiazole MAXWELL FINLAND, ELIAS STRAUSS and OSLER L PETERSON	1
Further Studies on Recurrences in Pneumococcic Pneumonia with Special Reference to the Effect of Specific Treatment ELIAS STRAUSS and MAXWELL FINLAND	17
Treatment of the Neuroses by Class Technic SAMUEL B HADDEN	33
The Rôle of the Vertebral Veins in Metastatic Processes. OSCAR V BATSON	38
A Study of the Hereditary Nature of Gout, A Report of Two Families C J SMYTH and R H FREYBERG	46
Chemotherapy of Pneumonias and Immunity Reactions JESSE G M BULLOWA, NATHAN H SCHACKMAN and DANIEL STATS	57
Protein Derivatives as Factors in Allergy ROBERT A COOKE	71
The Treatment of Acute Carbon Tetrachloride Poisoning with a Report of Two Cases BENJAMIN R ALLISON	81
A Theory Concerning the Manner in Which the Stomach Empties Itself WILLIAM TRAVIS GIBB, JR	94
The Pathological Physiology of the Early Manifestations of Left Ventricular Failure C SIDNEY BURWELL	104
The Cruveilhier-Baumgarten Syndrome, Review of the Literature and Report of Two Additional Cases EUGENE L ARMSTRONG, W L ADAMS, L J. TRAGERMAN and E W TOWNSEND	113
Case Reports	
Acute Hemolytic Anemia, Auto-Agglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy, Case Report ISADORE ROTHSTEIN and SIDNEY COHN	152
Hyperparathyroidism in a Patient with Acromegaly JULIUS CHASNOFF, LOUIS FRIEDFELD and ARTHUR M TUNICK	162
Editorial	176
Reviews	179
College News Notes	181

NUMBER 2, FEBRUARY, 1942

Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract II Hepatic Dysfunction JULES C ABELS, PAUL E REKERS, GEORGE E BINKLEY, GEORGE T PACK and C P RHOADS	221
Vitamin D in the Treatment of Infectious Arthritis CHARLES H SLOCUMB	241

Mental Symptoms Following Carbon Disulphide Absorption and Intoxication	FRANCIS J BRACELAND	246
Sulfanilamide in the Treatment of Erysipelas	LAWRENCE S SIEGEL, LEON ROSEVE and ALBERT G BOWER	262
Sulfadiazine and Sodium Sulfadiazine A Comparison of Certain of Their Clinical and Pharmacologic Values	CHARLES WHEELER and NORMAN PLUMMER	269
The Advantages and Clinical Uses of Desiccated Plasma Prepared by the Adtevac Process	J M HILL and E E MUIRHEAD	286
Observations on the Specific Treatment (Type A Antiserum) of Staphylococcal Septicemia, Second Report	L A JULIANELLE	303
William Withering His Contribution to Medicine	JONATHAN C MEAKINS	327
Case Reports		
Acute Hemolytic Anemia Caused by Sulfathiazole	JOSEPH J BUNIM and MURRAY ISRAEL	333
An Instance of Coronary Embolism in Subacute Bacterial Endocarditis	HARRY PARKS	339
Spontaneous Hemopneumothorax	DANIEL SNIVELY, HARRY SHUMAN and WILLIAM D SNIVELY	349
Sulfonamides and Heparin in the Treatment of Subacute Bacterial Endocarditis	LEO WAITZKIN, RICHARD H SMITH and WALTER B MARTIN	356
Uveoparotitis, A Report of Two Cases	WILLIAM HARBIN, JR and THOMAS S HARBIN	360
Editorial		366
Reviews		370
College News Notes		373
Program of the Twenty-Sixth Annual Session		385
University and Saint Paul Hospitals		406

NUMBER 3, MARCH, 1942

Exophthalmometric Measurements in Patients with Thyroid Diseases with Some Discussion of Their Significance	CARLOS GALLI-MAININI	415
Digitalis in the Prevention of Recurrent Cardiac Failure in Patients with Sinus Rhythm	M SOKOLOW, H B WEINBERG, J L PLAUT and L N KATZ	427
Gaucher's Disease I A Case with Hemolytic Anemia and Marked Thrombopenia, Improvement after Removal of Spleen Weighing 6822 Grams	HARRY MANDELBAUM, LOUIS BERGLER and MAX LEDLER	
II Lipid Analysis of the Gaucher's Spleen	ALBERT EDWARD SOBIE and IRVING ALAN KAYE	438
Electroencephalographic Changes during Hyperventilation in Epileptic and Non-Epileptic Disorders	NORMAN Q BRILL and HERTA SHIDIMANN	451

Certain Infections in the Background of Patients with Coronary Occlusion	JOHN T KING	462
Heterophile Antibody Reaction Caused by Bacterial Infection	S BORNSTLIN	472
The Treatment of Delirium Tremens with Faradic Shock Therapy, A New Approach Based upon the Psychobiological Concept	NATHANILL J BERKWITZ	480
Cardio-Pericardioplexy, The Surgical Treatment of Coronary Arterial Disease by the Establishment of Adhesive Pericarditis	SAMUEL ALCOTT THOMPSON and MILTON J RAISBECK	495
Electrostethography I Cathode Ray Visualization of Lung Chest Sounds	F LOWELL DUNN, WALTER E RAHM, JR and ROBERT M COCHRAN	521
Liver Function in Menstruation	ROBERT HEILIG and N L KANTENGAR	538
Case Reports		
Anuria Following Hemolytic Reaction to Blood Transfusion, Recovery Following Splanchnic Block	H RAYMOND PETERS	547
Equine Encephalomyelitis in a Laboratory Technician with Recovery	HERMAN GOLD and BETTYLEE HAMPIL	556
Non-Icteric Leptospirosis Icterohemorrhagia (Weil's Disease) Contracted while Bathing	PERK LEE DAVIS and MARGARET SHUMWAY DAVIS	569
Ventricular Fibrillation in Acute Coronary Artery Thrombosis during the Intravenous Administration of Quinidine Sulphate, Report of a Fatal Case	HAROLD L RAKOV	571
Editorial		577
Reviews		581
College News Notes		584
Minutes of the Board of Regents		599
St Paul		625

NUMBER 4, APRIL, 1942

The Emotional Component of the Ulcer Susceptible Constitution	GEORGE DRAPER	633
Sulfadiazine, A Study of Its Effect on Hemolytic Streptococci	CHARLES H RAMMELKAMP and CHESTER S KEEFER	659
Response to Sulfapyridine in 241 Cases of Pneumonia, with Special Reference to Lack of Prompt Response in Some Cases	SIDNEY SCHERLIS	666
The Cardiovascular Aspects of Carotid Sinus Hypersensitivity with Special Reference to Some Cardiac Arrhythmias	ALLEN D TANEY and ALFRED LILIENFELD	676
The Iron Content of the Skin in Hemochromatosis	HAROLD J MAGNUSON and B O RAULSTON	687

Meningococcal Meningitis, Report of Fifty Cases, Forty Treated with Serum and Ten Treated with Serum and Sulfanilamide	EUGENE P CAMPBELL	694
Fatigue of Patients with Circulatory Insufficiency, Investigated by Means of the Fusion Frequency of Flicker	NORBERT ENZER, ERNST SIMONSON and SAMUEL S BLANKSTEIN	701
Sulfonamides Passage into Spinal Fluid and Rectal Absorption	WINDSOR C CUTTING and ERNEST H SULTAN	708
Streptococcal Meningitis; Four Cases Treated with Sulfonamides in Which the Etiological Agent Was an Unusual Streptococcus	LOWELL A RANTZ	716
Recent Advances in the Care of the Comatose Patient	BARNETT A GREENE	727
The Concentration of Creatine in Heart, Diaphragm and Skeletal Muscle in Uremia	HARRY GROSS and MARTA SANDBERG	737
Observations on the Comparable Effects of Protamine Zinc and Regular Insulin in Diabetic Patients Followed over a Period of Years	ELAINE P RALLI, HAROLD BRANDALEONE and HARRY D FEIN	750
Convulsions in Paget's Disease, Electroencephalographic Observations	JOSEPH A MUFSON and PAUL CHODOFF	762
A Theory Explaining the Local Mechanism for Gastric Motor and Secretory Control and the Alteration of These Functions in Uncomplicated Duodenal Ulcer	HARRY SHAY, J GERSHON-COHEN and SAMUEL S FEIS	772
Case Reports		
Thrombocytopenic Purpura and Carcinoma of Stomach; Report of a Case with Purpura Appearing after Subtotal Gastrectomy	WILLARD H WILLIS	782
The Waterhouse-Friderichsen Syndrome Report of a Case in an Adult	A T KWEDAR	787
Editorial		792
Reviews		796
College News Notes		798

NUMBER 5, MAY, 1942

Gold Salts in the Treatment of Rheumatoid Arthritis, A Study of 245 Cases	RUSSELL L CFCIL, WILLIAM H KAMMERER and FRANCOIS J DEPRUME	811
The Manifestations in the Skin and Mucous Membranes in Dermatomyositis, with Special Reference to the Differential Diagnosis from Systemic Lupus Erythematosus	HARRY KEIL	828
Multiple Tests of Hepatic Function in Gastroenteric Malignancy, The Value of Bromsulphalein, Hippuric Acid and the van den Bergh Reaction in Detecting Hepatic Metastasis, with an Evaluation of Normality of the Hippuric Acid Test	MOSES PAULSON and CARL I WYIER	872

Some Effects of Potassium Salts in Man	NORMAN M KEITH, ARNOLD E OSTERBERG and HOWARD B BURCHELL	879
Treatment of Diabetes Mellitus with Protamine Insulin Is a Persistent Glycosuria Harmful? A Metabolic Study of a Severe Case	ED- WARD TOLSTOI, THOMAS P ALMY and VINCENT TOSCANI	893
Subacute Bacterial Endocarditis, An Analysis of Fifty Cases with Autopsy Findings	HAROLD COMONFORT DENMAN	904
Periarteritis Nodosa with Case Reports	GEORGE M JONES, JR	920
Anticipation and Diagnosis of Neurocirculatory Asthenia	JOHN T KING	941
The Clinical Manifestations and Diagnosis of Chronic Brucellosis	ROBERT C MANCHESTER	950
Status Dysraphicus and Syringomyelia	BERT E MULVEY and LEA A RIELY	966
Eosinophilia and Pneumonitis in Chronic Brucellosis, A Report of Two Cases	KENDALL A ELSON and FRANZ J INGELFINGER	995
Whither?	JAMES ALEXANDER MILLER	1003
Case Reports		
Masked Hyperthyroidism as a Cause of Heart Disease (with Report of a Case with Long Standing Auricular Fibrillation Cured by Subtotal Thyroidectomy)	SAMUEL H AVERBUCK	1011
Gonococcus Bacteremia with Joint and Skin Manifestations, Case Report	RUTH C FOSTER	1018
Editorial		1023
Reviews		1027
College News Notes		1029

NUMBER 6, JUNE, 1942

Addison's Disease Evaluation of Synthetic Desoxycorticosterone Ace- tate Therapy in 158 Patients	GEORGE W THORN, SAMUEL S DORRANCE and EMERSON DAY	1053
Primary Splenic Neutropenia, A Newly Recognized Syndrome, Closely Related to Congenital Hemolytic Icterus and Essential Thrombo- cytopenic Purpura	B K WISEMAN and C A DOAN	1097
Non-Operative Results in Ninety Patients with Abnormal Cholecysto- grams	STAIGE D BLACKFORD, ROBERT M BIRD, JR and S WARD CASSCELLS	1118
Heart Strain A Critical Review, The Development of a Physiologic Concept	AARON E PARSONNET and ARTHUR BERNSTEIN	1123
The Relationship of Upper Respiratory Infections to Rheumatic Activity in Chronic Rheumatic Heart Disease	IRVING R JUSTER	1137
Periarteritis Nodosa, Report of Five Cases	MORRIS M BANOWITCH, SILIK H POLAYES and RICHARD CHARET	1149
The Clinical Value of Sternal Bone Marrow Puncture	THEODORE H MENDELL, DAVID R MERANZE and THEODORE MERANZE	1180

A Pathological Study of the Significance of the Systolic Murmur	M S REDNICK	1197
Neuroblastoma (Sympathoblastoma or Neurocytoma) of the Suprarenal Medulla, Report of Three Cases	RALPH M THOMPSON	1206
Case Reports		
<i>H Influenzae</i> Bacteremia, Report of Two Cases Recovering Following Sulfathiazole and Sulfapyridine	CHESTER S KEEFER and CHARLES H RAMMELKAMP	1221
Brucella Endocarditis of Congenital Bicuspid Aortic Valve	HARRY F WECHSLER and EINAR G GUSTAFSON	1228
Infectious Mononucleosis and Encephalomyelitis	BURTON L ZOHMAN and EDMUND G SILVERMAN	1233
Uveoparotitis	MARIE L CARNS	1239
Chronic Meningococcemia Complicated by Acute Endocarditis	ROBERT B NYE, CHARLES W SEMISCH and LOUIS MERVES	1245
Editorial		1253
Reviews		1256
College News Notes		1258
Index		1267

ANNALS OF INTERNAL MEDICINE

VOLUME 16

JANUARY, 1942

NUMBER 1

ANTIBODY RESPONSE OF PATIENTS WITH PNEUMOCOCCIC PNEUMONIA TREATED WITH SULFADIAZINE AND SULFATHIAZOLE*

By MAXWELL FINLAND, M D , F A C P , ELIAS STRAUSS, M D , and
OSLER L. PETERSON, M D , *Boston, Massachusetts*

THE results of immunological studies of a large number of patients with pneumococcic pneumonia treated with sulfapyridine were reported recently from this laboratory.¹ As far as could be determined, the antibody response of these patients was comparable in every respect to that resulting from spontaneous recovery of similar cases included in previous investigations in which the same methods were employed.²⁻⁶ The tests used in the study of the serums from the sulfapyridine treated cases included agglutinins, which were determined in every instance, mouse protection tests, which were carried out in all cases due to some of the common pneumococcus types, and pneumococidal and opsonic tests, which were done only in a few cases.

Shortly after this paper was published, Kneeland and Mulliken⁷ reported on the antibody formation in 19 cases of lobar pneumonia treated with sulfapyridine. Employing only the precipitin reaction with type-specific polysaccharide, they demonstrated an excess of antibody in only four of the 19 cases, and even in these four cases antibodies were not noted until after the patients' temperature had been normal for about a week. They concluded that sulfapyridine has supplanted, at least to some degree, the immune mechanism in cases treated with this drug. They also felt that when antibody formation did occur in such cases it proceeded at a slower rate.

* Received for publication July 21, 1941.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston.

This study was carried out with the technical assistance of Mildred W. Barnes and Clare Wilcox. The chemical determinations were made by Elizabeth Shaler Smith and Alice N. Ballou.

than in untreated cases, probably because the stimulus to antibody formation was lessened through the action of the drug on the invading organism

In a subsequent paper⁸ the same authors, again employing only the precipitin test, demonstrated the appearance of an excess of type-specific antibody in 16 of 21 patients with lobar pneumonia treated with sulfathiazole. They interpreted their findings as indicating that there is a greater stimulus to antibody formation in patients treated with sulfathiazole than in those treated with sulfapyridine. This, in turn, led them to the conclusion that sulfapyridine was a more powerful antipneumococcal agent than sulfathiazole.

Because of the importance of these implications with respect to the general problem of the relation of modern chemotherapy to the immune response to infections, it was felt that, in view of the wide discrepancies in the results, further studies were necessary. In the present paper are presented the results of antibody studies in two groups of patients with pneumococcic pneumonia, one treated with sulfathiazole and the other treated with sulfadiazine. Sera from these patients taken at intervals during and after chemotherapy were tested for agglutinins and mouse protective antibodies against the homologous type pneumococci and for precipitins against the corresponding type-specific polysaccharide. This offered an opportunity to compare the results of the three tests in individual cases. These results, together with those previously reported, also permitted a comparison of the response of groups of patients treated with three different sulfonamide drugs.

MATERIALS AND METHODS

The patients studied were all admitted to the Boston City Hospital during the 1940-1941 season and all had clinical and roentgen-ray evidence of pneumonia. For the most part, patients with Types I, II, V and VIII pneumococci were chosen, since these were the frequently occurring types which have been found in this laboratory to be most satisfactory for mouse protection tests with sera of patients with pneumonia. A few cases with other types were included, but protection tests were not carried out with their serums. A blood culture was made in every instance before drug therapy was started. Sputum typings were made both before and after mouse inoculations. Similar dosages were used in almost all cases, namely, an initial dose of 2 or 4 grams followed by 1 gram every four hours until treatment was stopped. In a number of the sulfadiazine treated cases, however, the dose was reduced to 1 gram every six hours after essential recovery had taken place.

Blood for the serological tests and for the chemical determination of the concentration of the drug was obtained at frequent intervals during and after therapy. The *mouse protection tests* were carried out by the simultaneous inoculation of 0.2 c.c. of serum and decimal dilutions of stock strains of pneumococci which have been kept at maximum virulence by frequent mouse passage. The titers are recorded as the maximum number of fatal

doses protected by 0.2 c.c. of serum. No attempt was made to determine "end points" by using serial dilutions of the patients' serums. Some of the serums were tested with as much as 10^7 lethal doses (0.01 c.c. of culture), but as a rule 0.001 c.c. or 10^6 lethal doses was the largest amount of culture used. The protection of mice against the latter dose of culture by 0.2 c.c. of serum may be considered as the equivalent of 5 units per c.c. of serum. *Agglutinations* were done by mixing serial dilutions of serum with an equal volume of formalized saline suspension of a fully grown culture, incubating for two hours at 37°C and reading after overnight ice box storage. The titer was read as the final dilution of serum which produced grossly floccular agglutination. For the *precipitin tests*, both the method recommended by Bullock, Bukantz and de Gara⁸ and that used by Kneeland and Mulhiken⁹ were employed for a large number of the serums. Since qualitatively similar results were obtained with both these methods, only the latter was used in subsequent tests. Stock 1:1000 solutions of the type-specific polysaccharides were used.⁷ Preliminary titrations were made with serial saline dilutions of these antigens against serial dilutions of antipneumococcus rabbit serums of known potency. The latter dilutions were made in clear, normal human serum in order to approximate more nearly the conditions of the actual tests. The optimum dilution of the polysaccharides for detecting small amounts of antibody up to 100 units was found to be 1:50,000 and this dilution was therefore used routinely. In all instances final readings were made after an hour of incubation at 37°C and overnight ice box storage. All heavy precipitates were recorded as $++$, and definite positive tests with diluted serums were also classified as $++$. All other definite positive tests with undiluted serum are recorded as $+$ and those in which there was a very faint or doubtful precipitate were recorded as \pm . The agglutination and precipitin tests were controlled with antigens of heterologous types, and saline controls were also included in the precipitin tests. Chemical determinations of the drug concentration were carried out by the method of Bratton and Marshall¹⁰ with the aid of a Klett-Summerson colorimeter.

RESULTS

The results of the antibody studies in 48 patients who were treated with sulfadiazine alone and recovered are shown in table 1. The results in 46 similar cases treated with sulfathiazole are given in table 2. The more relevant data concerning the pneumonia and the therapy are also included in each instance. When several successive serums obtained from the same patient showed identical results, only the first and the last of such serums are listed. None of the patients included in these two tables received antipneumococcus serum or vaccines and, because of the known antigenicity of the type-specific pneumococcus carbohydrates when given intracutaneously,^{2,11} skin tests with specific polysaccharides were not done at any time.

⁸ Furnished by the Lederle Laboratories, Inc.

TABLE I
Patients Treated with Sulfadiazine

Number	Sex and age	Type	Sulfadiazine therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfadiazine (mg /100 ml)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
1	M 46	I	4	48	5	0	4 6 10	— 67 66	— 107 80	0 10 ⁵ 10 ⁶	0 0 4	0 0 ++
2	M 35	I	2	63	3	+	3 7 11 14	65 87 — —	79 98 — —	0 10 ⁵ 10 ⁵ 10 ⁵	0 2 2 0	0 0 0 0
3	F 18	I	3	32	4	+	9	—	—	10 ⁵	0	0
4	F 52	I	3	90	7	0	4 7 10 13 49	35 128 — — —	45 128 — — —	0 10 0 10 ⁵ 10 ⁵	0 0 0 4 2	0 0 0 + +
5	M 56	I	5	30	6	+	6 8 11	79 — —	87 — —	10 ⁴ 10 ⁵ 10 ⁶	0 0 +	0 0 +
6	M 33	I	4	26	6	0	6 8 10	83 80 —	92 80 —	0 0 0	0 0 0	0 0 0
7	M 38	I	3	30	4	+	3 4 6 8 11	— 95 137 — —	— 124 166 — —	0 0 10 ³ — 10 ³	0 0 0 0 0	0 0 0 ± +
8	M 10	I	3	18	5	+	5 7 9 18	— 57 — —	— 57 — —	0 10 ³ 10 ³ 10 ¹	0 0 2 2	0 0 + 0
9	M 31	I	5	26	6	0	7 10	— —	— —	10 ³ 10 ⁶	2 8	0 ++
10	M 76	I	3	27	4	0	5 9 11	80 — —	97 — —	10 10 10 ¹	0 0 0	0 0 0
11	F 52	I	4	50	5	0	4 6 8 10 12 14	0 — — — — —	0 — — — — —	0 10 10 ¹ 10 ¹ 10 ⁵ 10	0 0 0 0 0 2	0 0 0 + + +
							4 7 19	80 60 —	93 75 —	10 ³ 10 ⁴ —	0 16 4	0 ++ ++
							3 6 8 12	— 53 — —	— 53 — —	0 10 ¹ 10 ¹ 10 ¹	0 0 2 2	0 + + +

TABLE I (Continued)

Number	Sex and age	Type	Sulfadiazine therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Days begun	Amount (grams)			Days of disease	Blood sulfadiazine (mg /100 ml)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
14	M 38	I	2	30	3	0	5	8.5	9.9	10 ²	0	0
							7	7.9	9.0	10 ³	0	0
							9	7.7	8.8	10 ⁵	0	0
							11	0	0	10 ⁴	0	0
15	F 37	I	4	16	6	0	5	3.5	3.5	0	0	0
							7	5.6	6.6	0	0	0
							9	4.7	6.3	10 ²	0	0
							11	3.2	3.8	10 ⁶	4	++
14	—	—	10 ⁶	8	++							
16	M 38	I	2	75	3	0	9	5.8	6.4	10 ³	2	+
17	M 50	I	1	35	3	+	3	15.9	20.5	0	0	0
							5	12.6	15.4	10	0	0
							9	—	—	10 ⁶	0	0
							11	—	—	10 ⁵	0	0
18	F 43	II	2	30	4	0	5 8	6.4 —	7.8 —	10 ⁵ 10 ⁵	2 2	0 ++
19	M 10	II	2	59	2	+	2	—	—	0	0	0
							3	7.4	8.7	0	0	—
							6	6.4	7.6	10 ⁵	0	0
							9	5.2	6.3	10 ⁴	4	0
14	—	—	10 ⁴	4	0							
20	M 23	II	2	34	4	0	4	7.2	7.8	10 ⁴	0	0
							6	9.8	11.5	10 ⁶	16	++
							8	—	—	10 ⁷	64	++
							—	—	—	—	—	—
21	F 49	II	2	36	5	0	2	—	—	0	0	0
							5	5.2	5.2	0	0	0
							7	—	—	10 ²	0	0
							9	—	—	10 ⁶	8	++
14	—	—	10 ⁶	8	++							
22	F 42	II	2	57	4	0	3	9.4	9.4	0	0	0
							6	7.6	8.2	10 ⁵	2	0
							13	—	—	10 ⁶	4	++
							—	—	—	—	—	—
23	M 48	II	6	27	7	0	7	—	—	10 ⁴	2	+
							10	10.8	12.6	10 ⁶	8	+
							17	—	—	10 ⁵	8	+
							—	—	—	—	—	—
24	M 47	II	4	40	6	0	5	4.9	5.4	10 ²	0	0
							7	8.7	9.3	10 ⁶	16	±
							9	6.2	6.2	—	128	+
							11	3.7	4.3	10 ⁷	256	++
17	—	—	10 ⁶	64	+							
25	F 44	II	2	40	3	0	3	3.2	3.2	0	0	0
							5	6.9	7.5	10 ³	2	0
							7	5.9	6.6	10 ⁶	4	+
							9	—	—	10 ⁶	8	++
16	—	—	10 ⁶	8	+							

TABLE I (Continued)

Number	Sex and age	Type	Sulfa-diazine therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfadiazine (mg /100 ml)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
26	M 34	II	2	39	5	0	3	3.9	4.7	0	0	0
							5	12.6	16.0	10 ⁵	2	0
							7	8.3	9.6	10 ⁵	4	0
							9	—	—	10 ⁶	8	+
27	M 53	II	4	30	6	0	5	6.7	7.7	0	0	0
							6	7.7	8.3	0	0	0
							9	—	—	10 ³	2	+
							11	—	—	10 ⁷	4	+
28	M 49	V	3	32	4	0	5	9.6	10.7	0	0	0
							8	5.7	6.3	0	0	0
							11	—	—	10	0	0
							14	—	—	0	0	0
29	M 44	V	5	30	6	0	5	0.8	1.1	0	0	0
							10	5.1	6.7	10 ⁶	4	+
30	M 18	V	3	34	4	0	4	6.3	7.6	10 ³	0	0
							5	8.5	9.6	10 ⁵	0	0
							8	6.5	6.5	10 ⁵	2	0
							11	—	—	10 ⁵	2	+
31	M 16	V	4	54	6	0	5	4.5	5.4	0	0	0
							9	10.0	11.5	10 ⁵	2	0
							11	8.9	10.8	10 ⁶	8	0
							13	—	—	—	4	0
32	M 21	V	2	26	4	0	3	5.3	5.3	0	0	0
							5	9.8	11.9	10 ¹	0	0
							7	—	—	10 ⁶	4	+
33	M 37	V	2	29	4	0	4	8.7	9.9	0	0	0
							6	7.7	8.4	10 ³	0	0
							8	—	—	10 ¹	2	0
34	M 56	V	4	40	6	+	5	4.0	5.0	0	0	0
							7	8.5	9.4	10 ⁵	0	0
							9	6.8	6.8	10 ⁵	4	0
							13	—	—	—	16	++
							22	—	—	10 ⁶	16	++
35	M 50	V	5	33	7	0	6	5.2	6.7	0	0	0
							8	7.2	8.5	0	0	0
							10	7.9	8.7	10 ⁵	2	0
							14	—	—	10 ⁵	1	0
36	M 61	V	2	32	8	0	2	—	—	0	0	0
							4	7.6	10.0	0	0	0
							8	—	—	10 ⁵	1	++
							5	1.8	1.8	0	0	0
							7	6.0	6.0	10	2	+
							9	—	—	10 ⁵	16	++
							13	—	—	10 ⁷	64	++

TABLE 1 (Continued)

Sub- ject	Sex and age	Type	Sulfadiazine therapy		Day of crisis	Blood culture before treat- ment	Results of tests					
			Day begun	Amount (grams)			Day of dis- cuse	Blood sulfadiazine (mg /100 ml)		Mouse pro- tec- tion	Agglu- tinins	Precip- itins
								Free	Total			
38	M 15	VIII	4	30	5	+	6 9 11	10.8 7.2 —	12.8 7.2 —	0 10 10 ³	0 0 8	0 0 0
39	M 38	VIII	1	24	2	0	1 7 9	10.1 — —	11.1 — —	0 10 10 ¹	0 0 4	0 0 0
40	M 20	VIII	1	25	2	0	2 4 6 8	1.2 8.4 — —	5.2 10.8 — —	10 10 10 ² 10 ⁶	0 0 2 4	0 0 0 0
41	M 62	VIII	3	40	4	0	4 6 9 11	8.4 — — —	10.4 — — —	10 0 10 ² 10 ⁶	0 0 4 16	0 0 0 +
42	M 42	VIII	4	34	7	+	6 7 9 11 15	5.6 7.7 4.3 5.9 —	6.1 8.7 4.3 5.9 —	0 10 ² 10 ⁶ 10 ⁶ 10 ⁵	0 2 32 64 32	0 0 + ++ +
43	M 42	VIII	3	71	10	0	4 9 11 13 18	4.7 6.7 5.9 5.5 —	5.4 7.6 7.4 6.4 —	0 0 10 ³ 10 ² 10 ³	0 0 2 4 2	0 0 0 0 0
44	F 72	III	4	28	6	0	5 6 13	1.6 9.1 —	1.6 12.8 —	— — —	0 0 16	0 0 +
45	M 58	IV	4	60	9	0	4 6 8 10 12 14	— 11.7 6.7 — 7.3 —	— 13.1 6.7 — 8.1 —	— — — — — —	0 0 0 0 0 0	0 0 0 0 0 0
46	M 33	IV	3	38	6	0	3 5 8 14	5.1 6.0 7.3 —	5.1 7.8 8.4 —	— — — —	0 0 16 16	0 0 ++ ++
47	M 40	IV	4	32	7	0	5 6 8 10	4.8 11.6 7.2 —	4.9 13.7 8.2 —	— — — —	0 0 0 0	0 0 0 0
48	M 56	XVIII	2	37	6	+	2 3 6 8 11 14 18	— 4.9 3.6 — — — —	— 5.7 3.6 — — — —	— — — — — — —	0 0 0 0 4 2 0	0 0 0 0 0 0 0

TABLE II
Patients Treated with Sulfathiazole

Number	Sex and age	Type	Sulfa-thiazole therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of disease	Blood sulfathiazole (mg /100 ml)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
1	F 14	I	2	30	3	0	2 4 6	— 4.7 —	— 6.5 —	10 ² 10 ² 10 ⁵	0 — 2	0 — 0
2	M 47	I	7	25	8	+	13	—	—	10 ⁵	32	++
3	F 63	I	5	15	6	0	8 14 19	— — —	— — —	10 ⁶ 10 ⁶ —	4 16 16	++ ++ ++
4	F 30	I	5	30	7	0	6 8 11	— 6.0 —	— 6.6 —	10 ⁵ 10 ⁶ —	0 8 16	0 ++ ++
5	F 34	I	4	32	5	0	6	9.1	10.9	10 ⁵	2	+
6	M 33	I	6	39	7	0	6 8 10	— 2.0 2.6	— 2.0 2.6	10 ⁵ 10 ⁶ —	8 16 16	++ ++ ++
7	M 76	I	1	26	6	+	6 7 9 12 15	— 10.0 — — —	— 11.6 — — —	10 10 10 ³ 10 ³ 10 ²	0 0 0 2 4	0 0 0 0 +
8	M 57	I	5	25	8	0	6 8 10 14 20	— — — — —	— — — — —	0 0 10 ³ 10 0	0 0 0 0 0	0 0 0 0 0
9	F 35	I	5	23	7	0	6 9 13	4.4 — —	5.5 — —	10 ¹ 10 ² —	0 8 4	0 ++ ++
10	M 13	I	5	29	8	0	6 8 10 16	4.4 1.3 — —	5.7 5.7 — —	10 ² 10 ¹ 10 ⁵ —	0 0 1 1	0 0 ++ ++
11	F 21	I	1	31	3	0	2 3 5 7	4.0 5.8 1.8 —	1.6 7.0 5.8 —	0 0 10 10 ²	0 0 0 8	0 0 0 +
12	F 21	I	1	63	6	0	5 6 8 10 16 18	— 5.1 1.3 3.7 1.3 —	— 6.1 5.2 4.7 5.6 —	0 0 10 10 10 10	0 0 0 2 1 2	0 0 0 ++ ++ —
							7 8 10 12 16	2.6 5.9 1.0 5.8 —	2.6 1.9 1.9 1.1 —	0 10 10 10 ² 10	0 0 1 8 1	0 0 ++ ++ —

TABLE II (Continued)

Number	Sex and age	Type	Sulfathiazole therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (gram-)			Day of disease	Blood sulfathiazole (mg./100 ml.)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
14	F 48	I	3	33	4	0	3	—	—	0	0	0
							4	61	81	10 ⁴	0	0
							6	—	—	10 ⁵	4	+
							8	—	—	10 ⁵	16	+
							10	—	—	10 ⁶	16	++
							12	—	—	10 ⁶	16	+
							20	—	—	0	0	0
15	M 60	I	2	111	A	+	5	25	33	10 ³	0	0
							11	0	0	10 ⁶	16	++
							16	10	10	10 ⁶	8	++
16	M 40	I	3	50	5	+	4	60	77	0	0	0
							7	—	—	0	0	0
							10	25	31	10 ⁷	32	++
							14	—	—	10 ⁷	128	++
17	M 50	I	3	53	E	+	4	39	39	0	0	0
							5	45	52	0	0	0
							7	23	23	10 ⁵	4	+
							11	21	21	10 ⁶	32	+
							14	—	—	—	16	++
18	M 43	I	3	23	4	0	4	34	34	0	0	0
							6	—	—	10 ³	0	0
							8	—	—	10 ⁶	4	++
19	F 35	I	2	42	5	+	5	—	—	0	0	0
							7	40	48	0	0	0
							10	—	—	10 ²	0	0
							12	—	—	10 ²	0	0
							16	—	—	0	0	0
20	M 48	I	4	24	5	0	6	—	—	10 ³	0	0
							8	32	47	10 ⁴	0	0
							10	—	—	10 ⁶	8	++
21	M 39	II	3	41	4	0	3	—	—	0	0	0
							6	41	55	10 ⁶	8	++
							8	—	—	10 ⁷	32	++
							11	0	0	10 ⁷	64	++
							17	—	—	10 ⁶	32	+
22	M 28	II	4	33	5	0	5	65	79	0	0	0
							6	53	66	10 ³	0	0
							7	—	—	10 ⁵	2	+
							9	—	—	10 ⁵	2	++
							13	—	—	10 ⁶	8	+
23	M 32	II	2	30	4	0	2	—	—	10	0	0
							3	35	35	0	0	0
							5	—	—	0	0	0
24	M 37	II	5	43	7	+	7	39	46	10 ³	2	0
							9	18	18	10 ⁷	32	++
							11	—	—	10 ⁷	64	++
							17	—	—	10 ⁷	32	++

TABLE II (Continued)

Number	Sex and age	Type	Sulfa-thiazole therapy		Day of crisis	Blood culture before treatment	Results of tests					
			Day begun	Amount (grams)			Day of dis-ease	Blood sulfathiazole (mg /100 ml)		Mouse pro-tection	Agglu-tinins	Precip- itins
								Free	Total			
25	M 34	II	2	43	12	+	3	5.4	6.1	0	0	0
							5	5.0	6.2	0	0	0
							6	3.5	4.1	10 ⁵	0	0
							8	—	—	—	4	++
							14	—	—	10 ⁷	32	++
26	M 50	II	3	40	5	0	3	—	—	0	0	0
							5	4.0	5.1	0	0	0
							7	3.3	3.3	10 ⁴	2	0
							9	—	—	10 ⁴	8	+
27	M 67	II	3	25	5	0	3	—	—	0	0	0
							5	10.7	15.3	0	0	0
							7	4.7	7.0	0	0	0
							9	—	—	0	0	0
							12	—	—	10 ⁵	8	++
28	F 27	V	3	26	4	0	5	3.7	4.4	0	0	0
							7	3.4	4.4	10 ²	0	0
							30	—	—	10 ⁴	2	0
29	F 25	V	4	32	6	+	9	—	—	10 ⁵	2	0
30	M 18	V	2	23	4	+	3	1.3	1.3	0	0	0
							6	—	—	0	0	0
							9	—	—	10 ⁴	2	+
31	M 20	V	6	22	7	0	8	3.8	4.5	0	0	0
							10	—	—	10 ⁴	2	++
							15	—	—	10 ⁵	32	++
32	M 10	V	2	20	3	0	3	3.3	4.7	0	0	0
							4	—	—	10 ⁴	0	0
							6	—	—	10 ⁴	2	++
							8	—	—	10 ⁵	4	+
33	M 11	V	4	26	5	0	5	2.1	3.0	0	0	0
							6	2.3	3.3	10 ⁴	0	0
							8	2.8	4.1	10 ⁴	2	0
							10	—	—	10 ⁷	4	0
34	M 71	V	4	31	6	+	7	3.6	5.0	10 ⁴	2	0
							19	—	—	—	16	±
							13	—	—	10 ⁴	64	++
							17	—	—	—	32	++
35	M 41	V	5	37	6	0	5	—	—	10 ⁴	0	0
							8	4.5	6.5	10 ⁷	16	++
							10	3.9	5.0	—	32	++
							12	—	—	10 ⁷	64	++
36							6	5.1	8.0	0	0	0
							8	1.7	6.2	10 ⁴	8	0
							9	1.4	6.2	—	16	++
							11	6.1	8.1	10 ⁷	64	++

TABLE II (Continued)

No.	Sex & age	Type	Sulfathiazole therapy		Day of onset	Blood culture before treatment	Results of tests					
			Day begun	Amount given			Day of disease	Blood sulfathiazole (mg/100 ml)		Mouse protection	Agglutinins	Precipitins
								Free	Total			
37	M 53	VIII	1	35	3	0	2 6 8 10 12 20	5.6 — — — — —	7.6 — — — — —	0 10 0 0 10 0	0 0 0 0 0 0	0 0 0 0 0 0
38	M 17	VIII	3	24	1	0	5 7 9 11	3.6 4.1 — —	4.5 5.1 — —	0 10 10 ⁺ 10 ⁺	0 0 8 16	0 0 ± +
39	M 64	VIII	2	45	1	0	3 4 6 8 11 13	— 7.2 5.4 5.3 — —	— 8.8 7.4 6.1 — —	0 0 0 10 ⁺ 10 ⁺ 10 ⁺	0 0 0 4 32 64	0 0 0 0 ++ ++
40	M 39	III	7	128	E	0	9 12 14 16 18 23	1.9 1.5 — — — —	1.9 1.5 — — — —	— — — — — —	2 2 2 2 2 0	0 0 0 0 0 0
41	F 40	IV	2	35	3	0	3 6 8	— 5.1 7.4	— 6.2 9.4	— — —	0 0 2	0 0 0
42	F 23	IV	2	29	3	0	4 6 7 9	4.8 — — —	6.1 — — —	— — — —	0 2 4 4	0 0 0 ±
43	M 71	IV	2	35	6	0	3 5 7 9 11	3.4 5.3 5.1 — —	4.2 6.5 6.3 — —	— — — — —	0 0 0 0 0	0 0 0 0 0
44	F 32	XIV	1	17	5	0	2 5 7 9 11 13	1.9 0 — — — —	1.9 0 — — — —	— — — — — —	0 0 0 4 4 4	0 0 0 0 0 0
45	M 60	XIV	2	28	3	0	4 6 8	2.6 1.4 —	3.5 1.4 —	— — —	0 0 0	0 0 0
46	F 42	XIV	4	42	7	0	5 7 9 11 13	4.6 5.1 2.9 — —	5.2 6.6 3.7 — —	— — — — —	0 0 4 4 8	0 0 0 0 0

For explanation, see *Materials and Methods*
 — = test not done

A = arthritis (purulent)
 E = empyema

Almost all of the patients tested, both those treated with sulfadiazine and those who received sulfathiazole, developed mouse protective antibody about the time of essential clinical recovery (listed in the tables as the day of crisis) or later. In occasional cases these antibodies were found as early as the fourth day of the disease, but in the great majority of the cases they were not demonstrated until the sixth day or later. The maximum titers varied considerably. In most cases the titers were found to increase gradually over the course of a few days, while in others the titers rose more rapidly.

Agglutinins appeared in the serum either at the same time as the mouse protective antibody or later. They were demonstrated on the fifth day in occasional cases, but usually appeared on the seventh day or later. In no instance were agglutinins demonstrated in the absence of protection, although the reverse was frequently found. When the protective titer rose gradually the agglutinin titer usually followed. However, there was no strict quantitative correlation between the protective and agglutinin titers. In general, the results of the protection and agglutination tests were very similar to those previously obtained in patients treated with sulfapyridine.¹

The precipitin test with the homologous type-specific polysaccharide was the least sensitive of the three tests used. In general, the results of this test stood in about the same relation to the agglutinins as the latter did to the protective titers. In none of the sulfathiazole treated cases were precipitins demonstrated in the absence of agglutinins or before the appearance of the latter, but this did occur in occasional sulfadiazine treated cases. In such instances, however, moderate titers of mouse protection were present at the same time.

Patients with Multiple Types of Pneumococci. Pneumococci of other types, in addition to those noted, were identified in the sputum of nine of the patients listed in tables 1 and 2. Among the sulfadiazine treated patients Type IV pneumococci were found in case 11, Type XX in case 17, Type VII in case 18 and Type XV in case 35. Among the sulfathiazole treated patients, Type III pneumococci were identified in cases 19, 31 and 33, Type VIII in case 35 and Type XIX in case 40. The serums in these patients were tested for the presence of agglutinins for their respective type. In one of the patients (case 17, table 1), agglutinins for Type XX were found in a titer of 1:2 in each of the serums up to and including the ninth day, whereas in the next serum, obtained on the eleventh day, the titer was 1:8. In two sulfathiazole treated patients, Type III agglutinins were found in the first serum tested and the titers remained the same in later serums—in case 31 the titer was 1:4 and in case 33 the titer was 1:2. In the other six patients agglutinins were not demonstrated for the second pneumococcus type in any of the bloods obtained.

Cases Receiving Antipneumococcus Serum in Addition to Chemotherapy. In addition to the cases listed in tables 1 and 2, there were 14 patients with Type I, II, V or VIII pneumococcus pneumonia who received antipneu-

TABLE III
Maximum Titers of Antibodies in Recovered Cases of Pneumococcus Types I, II, V and VIII Pneumonia
Treated with Sulfadiazine, Sulfathiazole and Sulfapyridine

Drug	Type	No of Cases	Mouse protection					Agglutination				Precipitation		
			0 or 10	10 ⁰ or 10 ¹	10 ¹ or 10 ²	10 ² or 10 ³	10 ³ or 10 ⁴	0	2 or 4	8 or 16	32+	0	+	(±)
Sulfadiazine	I	17 [†]	1	2 ¹	8 ⁶	6 ¹	6 ³	8 ¹	3	0	6 ³	7 ¹	4	
	II	10 ¹	0	0	2 ¹	8	0	1 ¹	1	2	1 ¹	3	6	
	V	10 ¹	1	0	2	7 ¹	1	6	2 ¹	1	1	3	3 ¹	
	VIII	6 ²	0	2 ¹	1	3 ¹	0	3	2 ¹	1 ¹	4 ¹	1	1 ¹	
	Total	43 ¹¹	2	4 ²	13 ⁶	24 ³	7 ³	21 ⁶	11 ²	1 ¹	15 ³	11 ¹	14 ²	
Sulfathiazole	I	20 ⁶	0	2 ¹	6 ²	12 ¹	2 ¹	6 ¹	9 ¹	3 ²	3 ¹	1 ¹	13 ¹	
	II	7 ²	1	0	2	4 ²	1	0	3	3 ²	1	1	5 ²	
	V	8 ¹	0	0	3 ²	5 ¹	0	5 ²	3 ¹	0	3 ¹	1 ¹	4 ¹	
	VIII	4 ¹	1	0	0	3 ¹	1	0	1	2 ¹	1	1	2 ¹	
	Total	39 ¹²	2	2 ¹	11 ¹	24 ⁷	4 ¹	11 ³	16 ³	8 ⁶	8 ²	7 ²	24 ⁵	
Sulfapyridine *	I	19 ¹¹	1	2 ²	5 ³	11 ⁶	3 ¹	5 ¹	8 ¹	3 ²	3 ²	13 ¹		
	II	6 ¹	1	1	3	1 ¹	1	1	2	2 ¹	2 ¹	13 ¹		
	V	11	1	0	2	8	3	3	2	3	3	13 ¹		
	VIII	15 ²	3 ² †	6	5	1	3	7 ²	3	2	2	13 ¹		
	Total	51 ¹⁴	6 ²	9 ²	15 ³	21 ⁷	10 ¹	16 ⁶	15 ¹	10 ¹	10 ¹	13 ¹	Not done	

Superscripts represent the numbers of patients who had positive blood cultures before treatment

* Summarized from previous report by Finland, Spring and Lowell¹

† The 2 bacteremic patients each acquired mouse protective antibody against 10 LD

mococcus serum after one to five days of chemotherapy and whose bloods were tested for antibodies. Eight of these patients were treated with sulfadiazine and six with sulfathiazole. Antibodies were demonstrated in only three of the 14 patients in the blood obtained before the first dose of serum was given. One patient treated with sulfadiazine developed agglutinins and protective antibodies but not precipitins, whereas in another treated with this drug and in one treated with sulfathiazole the antibodies were demonstrable by all three tests before antiserum was administered. In the remaining 11 patients no antibodies could be demonstrated at this time. In all the 14 patients, including three who died, high titers of agglutinins, precipitins and mouse protection for the homologous pneumococcus were found in all the bloods obtained after the antiserum was given.

Comparison of Antibody Response in Patients Treated with Three Different Sulfonamides. The maximum titers of antibodies obtained in all the recovered cases of sulfadiazine and sulfathiazole treated Types I, II, V and VIII pneumococcus pneumonia are summarized in table 3. In this table is also included a summary of the results of protection and agglutination tests in the corresponding sulfapyridine treated cases previously reported.¹ There was no significant difference in the results obtained in each of the three groups of cases. This is best seen by comparing the results of the mouse protection tests in the Type I cases. While some variations are noted among the other types, they are not great considering the limited numbers of cases and the large number of variables involved.

DISCUSSION

The data presented indicate that, generally speaking, the antibody response of patients with pneumococcus pneumonia who recover following treatment with effective sulfonamide drugs is the same regardless of the drug used. Furthermore, a comparison of these results with the results of comparable studies in similar patients without chemotherapy or specific serotherapy indicates that the antibody response is not influenced by chemotherapy. This is in accord with the findings in experimental pneumococcal infections in mice treated with sulfapyridine from which McIntosh and Whitby¹² concluded that "The administration of sulphonamide drugs has no stimulating action on the body defences, nor does such administration affect the quality, quantity, or speed of production of recognised specific antibodies." Levine, Larson and Bieter¹³ likewise demonstrated the development of a high degree of specific immunity in rabbits experimentally injected with virulent pneumococci and treated with sulfapyridine. The latter authors began chemotherapy one hour after the infection was produced. They also demonstrated the development of a species-specific immunity which is explicable on the basis of their choice of the intracutaneous route for the infections.⁴

The conclusions of Kneeland and Mulliken^{7,8} with respect to the effect of chemotherapy on the antibody response to pneumococcic infections are not in agreement with the results of the present studies or with those previously reported.¹ Likewise, their conclusion that sulfapyridine is a somewhat more powerful antipneumococcal agent than sulfathiazole has not been borne out by the accumulated experimental and clinical data.

SUMMARY AND CONCLUSIONS

Antibody studies were carried out in two groups of patients with pneumococcic pneumonia, one treated with sulfadiazine and the other treated with sulfathiazole.

The antibody response in these two groups of patients was very similar, as judged by the results of the mouse protection, agglutinin and precipitin tests.

The results of mouse protection and agglutinin tests in these two groups of cases were essentially the same as those previously reported in sulfapyridine-treated cases and in patients who recover without specific serum or chemotherapy.

The precipitin test with type-specific polysaccharide is the least sensitive of the three tests employed in this study as a measure of antibody production in patients with pneumococcic pneumonia, the mouse protection test is the most sensitive and the agglutination test is intermediate.

REFERENCES

- 1 FINLAND, M, SPRING, W C, and LOWELL, F C Immunological studies on patients with pneumococcic pneumonia treated with sulfapyridine, *Jr Clin Invest*, 1940, xix, 179
- 2 FINLAND, M, and SUTLIFF, W D Specific cutaneous reactions and circulating antibodies in the course of pneumonia I Cases receiving no specific therapy, *Jr Exper Med*, 1931, liv, 637
- 3 FINLAND, M, and WINKLER, A W Antibody response to infections with Type III and the related Type VIII pneumococcus, *Jr Clin Invest*, 1934, xiii, 79
- 4 *Idem* Antibody response to infections with Type II and the related Type V pneumococcus, *Ibid* p 97
- 5 WINKLER, A W, and FINLAND, M Antibody response to infections with the newly classified types of pneumococci (Cooper), *Ibid*, p 109
- 6 FINLAND, M, TILGHMAN, R C, RUEGSEGGER, J M, and DOWLING, H F Clinical and immunological observations in cases of pneumococcus Type VII pneumonia treated with type-specific antibody, *Am Jr Med Sci*, 1937, cxciii, 59
- 7 KNEELAND, Y, and MULLIKEN, B Antibody formation in cases of lobar pneumonia treated with sulfapyridine, *Jr Clin Invest*, 1940, xix, 307
- 8 *Idem* Antibody formation in cases of lobar pneumonia treated with sulfathiazole, *Ibid*, p 735
- 9 BULLOWA, J G M, BUKANTZ, S C, and DE GARA, P F The balance between capsular polysaccharide and antibody in relation to prognosis and therapy in pneumococcal pneumonia, *ANN INT MED*, 1941, xiv, 1348
- 10 BRATTON, A C, and MARSHALL, E K, JR A new coupling component for sulfanilamide determination, *Jr Biol Chem*, 1939, cxxviii, 537

11. (a) FRANCIS, T, and TILLET, W S . Cutaneous reactions in pneumonia The development of antibodies following intradermal injection of type-specific polysaccharides, Jr Exper. Med , 1930, lii, 573
(b) FINLAND, M and SUTLIFF, W D Specific antibody response of human subjects to intracutaneous injection of pneumococcus products, *Ibid* , 1932 lv, 853
(c) FINLAND, M, and DOWLING, H F . Cutaneous reactions and antibody response to intracutaneous injections of pneumococcus polysaccharides. Jr. Immunol . 1935, xxix 285
(d) FINLAND, M, and BROWN, J W Reactions of human subjects to the injection of purified type-specific pneumococcus polysaccharides, Jr Clin Invest 1938 xvi, 479
- 12 MCINTOSH J, and WHITBY, L E H The mode of action of drugs of the sulphonamide group, Lancet 1939, i, 431
- 13 LEVINE, M LARSON, W P, and BIETER, R N Active immunity to pneumococci in rabbits protected by sulfapyridine, Proc. Soc. Exper. Biol and Med, 1939, xlii, 515
- 14 JULIANELLE, L A Reactions of rabbits to intracutaneous injections of pneumococci and their products I The antibody response, Jr Exper Med., 1930, li, 441 II Resistance to infection *Ibid* p 449

FURTHER STUDIES ON RECURRENCES IN PNEUMOCOCCIC PNEUMONIA WITH SPECIAL REFERENCE TO THE EFFECT OF SPECIFIC TREATMENT

By ELIAS STRAUSS, M D , and MAXWELL FINLAND, M D , F A C P ,
Boston, Massachusetts

In a previous paper Finland and Winkler¹ presented an analysis of 57 cases with recurrent attacks of pneumococcic pneumonia. Most of these cases occurred before the present classification of pneumococci² came into use. In a large proportion of the cases, the pneumococci were, therefore, classified as Group IV. Since that time, a much larger group of cases has been accumulated. Pneumococcus typing has improved in efficiency as a result of the introduction of the Neufeld method³ and of the more complete classification of the types. Much new information also has been gained about the "higher" types of pneumococci, especially with respect to their rôle in carrier states and as incitants of disease. During this period, moreover, profound changes have occurred in the treatment of pneumonia. The use of specific antipneumococcic serums for types other than I and II and, in the past three years, the introduction and extensive employment of sulfonamide drugs have appreciably altered the course and outcome of attacks of pneumococcic pneumonia. The present study was undertaken in an attempt to determine whether any definite change has occurred in the incidence or character of the recurrences in pneumonia as a result of the improved bacteriologic methods, the extended knowledge of pneumococcus types and newer methods of treatment.

SELECTION OF CASES

The patients were treated for all their attacks at the Boston City Hospital and, in all but a few instances, they were treated on the Medical Services to which are admitted only patients over 12 years of age. No patient included in the first report is considered here unless he subsequently had another attack of pneumococcic pneumonia. Each patient had two or more distinct attacks of pneumonia with characteristic physical and roentgenographic findings during each attack. One or more types of pneumococci were isolated and identified serologically during each attack. Each patient was discharged and well before the onset of the succeeding attack, this arbitrary criterion being used to distinguish "recurrence" from "relapse." Attacks of pneumonia

* Received for publication August 21, 1941.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston.

in which pneumococci were not isolated were excluded. The usual methods were employed for the isolation and typing of pneumococci.

ANALYSIS OF CASES

The following features of the cases will be considered: Age, sex and color, the number, character, and location of the pulmonary lesions in the recurrent as compared with the initial attacks, the interval between attacks, the pneumococcus types, the occurrence of positive blood cultures, the mortality in the recurrences, and the influence of the various kinds of therapy on the duration of disease and the frequency of recurrences. A limited number of observations regarding antibodies is also included.

Age, sex and color. Of the 168 patients with recurrent attacks of pneumococcic pneumonia all but one (aged 4) were over 13 years of age, and 37 were 50 years of age or older at the time of the initial attack. Forty-eight, or 26.2 per cent, of the patients were females. All but 12 were white.

Number of recurrences. The 168 patients had 191 recurrent attacks of pneumococcic pneumonia. In each of four patients, there were four recurrences (five attacks); in 14 cases there were two recurrences (three attacks); and the remaining patients each had a single recurrent attack. In the various tabulations, each recurrence is correlated with the initial attack unless otherwise indicated.

Character of the pulmonary lesion. In the initial attack 128, or 76 per cent, of the patients had lobar pneumonia and 40, or 24 per cent, had an atypical pulmonary lesion. Of the 191 recurrent attacks, 132 or 69 per cent were lobar pneumonia. The character of the lesion in the first attack and in each of the succeeding attacks in the same patient are compared in table 1.

TABLE I

Comparison of Pulmonary Lesions in First Attacks and in Recurrences

First Attack	Recurrence	Number	Per Cent
Lobar	Lobar	113	59
Lobar	Atypical	34	18
Atypical	Lobar	19	10
Atypical	Atypical	25	13
Total recurrences		191	100

Nearly three-fifths of the patients had lobar pneumonia in both the initial and the recurrent attacks. In less than 30 per cent of all the attacks the character of the lesion was different in the first and in subsequent attacks in the same patient.

Location of the pulmonary lesions. In table 2 the lobes involved in the initial and the recurrent attacks are compared. Eleven recurrences (of the total of 191) were omitted for lack of pertinent data. The frequency with

TABLE II

Comparison of Lung Involvement During First and Recurrent Attacks of Pneumococcus Pneumonia

Lung Involved During First Attack		Lung Involved During Recurrence									Total First Attack	
		Right Lung				Left Lung				Bi-lateral		
		Lower	Upper and/or Middle	Entire	Total	Lower	Upper	Entire	Total			
<i>Right</i>												
Lower		18	10	0	28	9	1	1	11	11	50	28
Upper and/or Middle		7	3	0	10	4	0	0	4	1	15	8
Entire		3	2	1	6	5	0	0	5	1	12	7
Total		28	15	1	44	18	1	1	20	13	77	43
<i>Left</i>												
Lower		16	11	3	30	14	4	1	19	8	57	32
Upper		1	1	0	2	1	1	0	2	0	4	2
Entire		1	1	1	3	0	1	0	1	0	4	2
Total		18	13	4	35	15	6	1	22	8	65	37
Bilateral		11	3	2	16	6	0	0	6	13	35	20
Total Recurrences	No	57	31	7	95	39	7	2	48	34	177	—
	%	32	18	4	54	22	4	1	27	19	—	100

which the various lobes were involved, both in the initial attack and in the recurrences, was not essentially different from what has been found in large series of unselected cases of pneumococcic pneumonia⁴. There was no tendency for the recurrence to involve the lobe affected in the first attack more than any other lobe. The incidence of bilateral involvement in the early and later attacks was nearly identical. The recurrences, therefore, tended to be neither more localized nor more extensive than the initial attacks.

Secondary pneumonias Chronic pulmonary disease to which the attacks of pneumonia were thought to be secondary was present in 25, or 15 per cent of the patients. Eight patients had chronic bronchiectasis, 13 had chronic passive congestion of the lungs due to various types of heart disease, two had chronic pulmonary tuberculosis, one had a lung abscess, and another had Boeck's sarcoid involving the lungs. These 25 patients accounted for 32 recurrent attacks. Only three had more than two attacks. Two of the three subjects who each had five attacks of pneumonia had bronchiectasis.

Interval between attacks (table 3) The shortest interval between essential recovery from one attack and the onset of another was seven days, the longest was 18 years. Of the 12 recurrent attacks which occurred within two months of the preceding attack, eight were in subjects with bronchiec-

TABLE III
Interval Between Attacks of Pneumococcus Pneumonia

Interval	Number of Attacks	Number of Attacks with Same Type in Successive Attacks
Less than 2 months	12	6
2 to 6 months	27	11
6 to 12 months	27	4
1 to 3 years	59	10
3 to 5 years	36	5
5 to 10 years	20	1
10 or more years	10	0
Total	191	37 (19.4%)

tasis, and in four of these eight the same type of pneumococci was isolated in each of two successive attacks. Of the 27 recurrences after two to six months, 12 were in subjects with chronic pulmonary disease, but only two of these were recurrences with the same type of pneumococcus in successive attacks. Of the 153 attacks that recurred after six months, only 12 were in patients with chronic pulmonary disease. It is usually thought that patients with chronic pulmonary disease are more likely to have recurrences of pneumonia at shorter intervals than those with otherwise normal lungs.

Altogether, the same type of pneumococcus was isolated in two successive attacks in the same subject in 37 of the 191 recurrences, or 19 per cent. In the 39 instances in which successive attacks occurred within six months, the same type was obtained both times in 17, or 46 per cent, while in the successive attacks that were more than six months apart, the same type occurred in 20 of 152 cases, or 13 per cent. In other words, successive attacks were associated with the same pneumococcus type three and one-half times as often if they occurred less than six months apart than if they occurred more than six months apart. As the interval between attacks increased, the frequency with which the same pneumococcus type appeared in successive attacks decreased progressively. This was equally true for patients with and for those without underlying chronic pulmonary disease. This may imply that persistence of pneumococci either in the carrier state or in foci of infection, rather than exogenous reinfection, accounts for a large proportion of the early recurrences of pneumonia with the same type of pneumococcus. Although in the majority of convalescent patients the homologous pneumococci disappear in a few weeks,⁵ it is known that they may persist for as long as 25 months after an attack of pneumonia.⁶

Pneumococcus types The frequency with which various types of pneumococci were isolated during the first and subsequent attacks is listed in table 4. The types in each of 20 patients in whom multiple types of pneumococci were isolated during one or more attacks are excluded from this table and shown separately in table 5. These results may be compared with data on a large number of cases of pneumococcic pneumonia reported from

TABLE III

Interval Between Attacks of *Pneumococcus Pneumonia*

Interval		Number of Attacks	Number of Attacks with Same Type in Successive Attacks
Less than 2 months	12	6	
2 to 6 months	27	11	
6 to 12 months	27	4	
1 to 3 years	59	10	
3 to 5 years	36	5	
5 to 10 years	20	1	
10 or more years	10	0	
Total	191	37	(19.4%)

tasis, and in four of these eight the same type of pneumococci was isolated in each of two successive attacks. Of the 27 recurrences after two to six months, 12 were in subjects with chronic pulmonary disease, but only two of these were recurrences with the same type of pneumococcus in successive attacks. Of the 153 attacks that recurred after six months, only 12 were in patients with chronic pulmonary disease. It is usually thought that patients with chronic pulmonary disease are more likely to have recurrences of pneumonia at shorter intervals than those with otherwise normal lungs.

Altogether, the same type of pneumococcus was isolated in two successive attacks in the same subject in 37 of the 191 recurrences, or 19 per cent. In the 39 instances in which successive attacks occurred within six months, the same type was obtained both times in 17, or 46 per cent, while in the successive attacks that were more than six months apart, the same type occurred in 20 of 152 cases, or 13 per cent. In other words, successive attacks were associated with the same pneumococcus type three and one-half times as often if they occurred less than six months apart than if they occurred more than six months apart. As the interval between attacks increased, the frequency with which the same pneumococcus type appeared in successive attacks decreased progressively. This was equally true for patients with and for those without underlying chronic pulmonary disease. This may imply that persistence of pneumococci either in the carrier state or in foci of infection, rather than exogenous reinfection, accounts for a large proportion of the early recurrences of pneumonia with the same type of pneumococcus. Although in the majority of convalescent patients the homologous pneumococci disappear in a few weeks,⁶ it is known that they may persist for as long as 25 months after an attack of pneumonia.⁶

Pneumococcus types The frequency with which various types of pneumococci were isolated during the first and subsequent attacks is listed in table 4. The types in each of 20 patients in whom multiple types of pneumococci were isolated during one or more attacks are excluded from this table and shown separately in table 5. These results may be compared with data on a large number of cases of pneumococcic pneumonia reported from

TABLE III
Interval Between Attacks of Pneumococcus Pneumonia

Interval	Number of Attacks	Number of Attacks with Same Type in Successive Attacks
Less than 2 months	12	6
2 to 6 months	27	11
6 to 12 months	27	4
1 to 3 years	59	10
3 to 5 years	36	5
5 to 10 years	20	1
10 or more years	10	0
Total	191	37 (19.4%)

tasis, and in four of these eight the same type of pneumococci was isolated in each of two successive attacks. Of the 27 recurrences after two to six months, 12 were in subjects with chronic pulmonary disease, but only two of these were recurrences with the same type of pneumococcus in successive attacks. Of the 153 attacks that recurred after six months, only 12 were in patients with chronic pulmonary disease. It is usually thought that patients with chronic pulmonary disease are more likely to have recurrences of pneumonia at shorter intervals than those with otherwise normal lungs.

Altogether, the same type of pneumococcus was isolated in two successive attacks in the same subject in 37 of the 191 recurrences, or 19 per cent. In the 39 instances in which successive attacks occurred within six months, the same type was obtained both times in 17, or 46 per cent, while in the successive attacks that were more than six months apart, the same type occurred in 20 of 152 cases, or 13 per cent. In other words, successive attacks were associated with the same pneumococcus type three and one-half times as often if they occurred less than six months apart than if they occurred more than six months apart. As the interval between attacks increased, the frequency with which the same pneumococcus type appeared in successive attacks decreased progressively. This was equally true for patients with and for those without underlying chronic pulmonary disease. This may imply that persistence of pneumococci either in the carrier state or in foci of infection, rather than exogenous reinfection, accounts for a large proportion of the early recurrences of pneumonia with the same type of pneumococcus. Although in the majority of convalescent patients the homologous pneumococci disappear in a few weeks,⁵ it is known that they may persist for as long as 25 months after an attack of pneumonia.⁶

Pneumococcus types The frequency with which various types of pneumococci were isolated during the first and subsequent attacks is listed in table 4. The types in each of 20 patients in whom multiple types of pneumococci were isolated during one or more attacks are excluded from this table and shown separately in table 5. These results may be compared with data on a large number of cases of pneumococcic pneumonia reported from

this hospital for the period from 1929 to 1936? This comparison has the advantage that the cases in both series were drawn from the records of the same hospital, and, to a certain extent, in the same period of time. In that report, 79 per cent of 2229 cases of lobar pneumonia were associated with pneumococci of types I, II, III, V, VII and VIII, while 21 per cent were

TABLE IV

Comparison of Predominant Types of Pneumococcus Recovered During First Attack and During Recurrence

Type	First Attack		Recurrence		Number with Same Type in First Attack and Recurrence
	Number	Per Cent	Number	Per Cent	
I	31	18.7	18	10.8	4
II	19	11.4	16	9.6	3
III	26	15.7	20	12.0	9
V	7	4.2	6	3.6	0
VII	11	6.6	12	7.2	0
VIII	12	7.2	13	7.8	2
Types I, II, III, V, VII, VIII	106	63.9	85	51.2	18
IV	3	1.8	8	4.8	0
VI	8	4.8	5	3.0	0
IX	3	1.8	3	1.8	0
X	6	3.6	2	1.2	0
XI	6	3.6	2	1.2	0
XII	2	1.2	6	3.6	0
XIII	2	1.2	0	0	0
XIV	5	3.0	7	4.2	1
XV	2	1.2	3	1.8	0
XVI	1	0.6	2	1.2	0
XVII	1	0.6	5	3.0	0
XVIII	6	3.6	1	0.6	1
XIX	3	1.8	12	7.2	1
XX	2	1.2	11	6.6	0
XXI	1	0.6	3	1.8	0
XXII	1	0.6	0	0	0
XXIII	1	0.6	1	0.6	0
XXV	3	1.8	2	1.2	0
XXVII	0	0	1	0.6	0
XXVIII	0	0	2	1.2	0
XXIX	0	0	2	1.2	0
XXXI	1	0.6	2	1.2	0
XXXII	2	1.2	0	0	0
Unclassified	1	0.6	1	0.6	0
All "Higher types"	60	36.1	81	48.8	3
Total	166	100	166	100	21

associated with other types (IV, VI, IX-XXXII). In the present study, 64 per cent of the first attacks were associated with types I, II, III, V, VII and VIII while in the recurrences only 51 per cent of the cases had pneumococci of these six types. This might imply that the type distribution in the present series of cases was atypical in that there was in each instance a

larger proportion of "higher" types. However, as already noted, 24 per cent of the initial attacks were atypical or bronchopneumonias, and 31 per cent of the recurrent attacks were in that category. In the series referred to previously,⁷ it was found that only 43.9 per cent of 619 cases of atypical pneumococcic pneumonia were associated with types I, II, III, V, VII and VIII. In the present cases there was a somewhat greater proportion of atypical pneumonias in the recurrences than in the initial attacks. When due allowance is made for this factor, the type distribution in both the initial

TABLE V

Multiple Types of Pneumococci Isolated During One or More Attacks of Pneumonia

Case Number	Pneumococci Isolated		Associated Disease
	First Attack	Recurrence	
4	BMC	(1) IX, XIX, BMC (2) XXIX, BMC (3) IX, XVI, BMC (4) IX, XVI, XXIX XXXIII, BMC	Bronchiectasis
22	III	IX, XXIX	Lung Abscess
28	VII, XIII	V	
31	VII, VIII	V, VIII	
39	III	III, X	
41	X	VII, XXVIII	
46	XVI	XI, XVI, XVII	C P C Emp (first attack) C P C
54	VIII (BC), XXIX (Emp)	XXII	
59	III	III, I (BC)	
60	XVIII	I, XVIII	
72	III, X	III	
78	I	(1) IV (2) VII (3) III, XI (4) III, V	C P C Bronchiectasis
91	III	XIX, XXVII	
103	III, XI, XVII	III, VIII, XV	
108	XVI, XXXII	VII	
133	I	XXII, XXIX	
151	VIII	VIII, XX, XXIX	
171	VI, VIII	XV, XIX	
184	VII, XXIX	XII, XVII, XXIX	
187	I	X, XIII	

BMC = Friedlander bacillus, type 1

BC = blood culture

Emp = empyema

C P C = chronic passive congestion of lungs due to heart disease of various types

and recurrent attacks was about what might be expected in a series of unselected cases including both lobar and atypical pneumonias.

The number of instances in which the same type of pneumococcus was isolated in both the initial and recurrent attacks in the same patient was too small for the percentage distribution of types to be of particular significance. Nevertheless, the proportion of Types I and II was about what would be expected on the basis of the usual frequency of occurrence of these types in

pneumonia. Type III, however, accounted for 14 of the 37 cases with the same type in both attacks. At least two explanations are suggested for this high incidence of recurrences with this type. Type III is known to be one of the most frequent types isolated from healthy carriers.⁹ In addition, there is reason to expect reinfection with this type frequently, since nearly one-third of the cases of Type III lobar pneumonia at autopsy were found to have gross or microscopic abscess formation in the lungs.⁹

In some cases in the present series, pneumococci were associated with other organisms including Friedlander's bacillus, influenza bacilli, staphylococci and hemolytic streptococci. The relation of the pneumococci to the etiology of the pneumonia, in some of these cases, may be open to some doubt.

In table 5, the cases with multiple types of pneumococci in one or more attacks are listed. In case 4, an example of chronic Friedlander's bacillus infection of the lungs, the various types of pneumococci were probably of little etiological significance. It has been pointed out that other organisms, including pneumococci, tend to appear in the sputum of patients with chronic Friedlander's bacillus pneumonia.¹⁰ In seven of these 20 cases, the existence of chronic pulmonary disease made it likely that some, if not most, of the multiple types of pneumococci found were carrier types. The frequency with which certain types appeared in this group of cases was notable. Type III was found 12 times, Type VII, five times, VIII, six times, XVI, four times, and XXIX, seven times. The frequent presence of these types in repeated attacks of pneumonia suggests strongly that they were carrier types.

In a few cases, both types isolated in a single attack of pneumonia appeared to be significant organisms. Thus, in case 54, Type VIII was isolated from the blood and Type XXIX from empyema fluid. In case 60, in the first attack Type XVIII was present in the sputum while in the recurrence Types I and XVIII were present in both sputum and empyema fluid.

Bacteremia. A record of one or more blood cultures taken during the initial attack was available in 135 cases. Eighteen of these were positive for pneumococci, a bacteremic rate of 13.3 per cent. In the 191 recurrences, the results of blood cultures were recorded in 179, 29 were positive for pneumococci, or 16.2 per cent. To make a valid comparison between the two groups, however, the fatal recurrences had to be excluded. The corrected bacteremic rate for recurrent attacks which ended in recovery was then 13.1 per cent. There was, therefore, no difference between the incidence of bacteremia in initial attacks and in non-fatal recurrences. Moreover, these rates are similar to the incidence of bacteremia reported in a series of 853 non-fatal cases of pneumonia in this hospital.¹¹

Five patients had bacteremia in both the first and subsequent attacks. Only one patient had bacteremia of the same type (II) in successive attacks, and these occurred 12 months apart. The following types were involved in successive attacks in the other four patients: V and XIX, XI and XIV, II and VII, and VIII and III. One other patient had bacteremia with Type

XII in the second attack, and Type XI in the third attack, but a negative blood culture in the initial attack

Mortality There were 21 deaths in 191 recurrent attacks of pneumonia, a mortality of 11 per cent. This is considerably lower than the average during the period of this study in this hospital. In 112 of these recurrent attacks, specific therapy in the form of antipneumococcus serums, sulfonamide drugs (sulfapyridine, sulfathiazole and sulfadiazine), or a combination of serum and sulfonamides was used. The mortality in this specifically treated group was 11.6 per cent. In 79 attacks in which no specific treatment was given the mortality was 10.1 per cent. Although the proportion of subjects over 50 years of age and those with multiple lobe involvement was approximately the same in both treated and untreated groups, the former had a bacteremic rate of 21 per cent while in the untreated cases, the bacteremic rate was only 6 per cent. It is obvious that the subjects who were treated were, on the whole, more seriously ill on admission and would be expected to have a higher mortality rate. Some of the patients who received no specific therapy were already recovering from their attack at the time of admission to the hospital.

Eight of the 29 patients who had bacteremia during recurrent attacks died. Of these 29 patients, 23 were treated with specific therapy and four died, of the five untreated bacteremic patients, three died. Two-thirds of the 21 patients who died were over 50 years of age. Five patients died of complicating diseases independent of the pneumonia.

Duration of acute disease in non-fatal attacks The duration of acute illness during initial and subsequent attacks was one indication of the relative severity of recurrent pneumonia. In making such a comparison the effect of treatment of each attack was considered since specific therapy might be expected to modify the duration of an attack. In table 6, 128 initial attacks

TABLE VI
Duration of Acute Illness (Non-fatal Attacks) in Relation to Therapy

Therapy of First Attack	Number of Cases	Recurrence							
		No Specific Therapy				Specific Therapy			
		Duration Same within 2 Days in Both Attacks	Recurrence 2 or More Days Longer	Recurrence 2 or More Days Shorter	Total	Duration Same within 2 Days in Both Attacks	Recurrence 2 or More Days Longer	Recurrence 2 or More Days Shorter	Total
No specific therapy	80	12 (38%)	4 (19%)	14 (44%)	32 (100%)	14 (29%)	6 (13%)	28 (58%)	48 (100%)
Specific therapy	48	6 (46%)	5 (39%)	2 (15%)	13 (100%)	21 (60%)	6 (17%)	8 (23%)	35 (100%)
Total	128	18	11	16	45	35	12	36	83

and the same number of non-fatal recurrences were compared. Twenty-one fatal attacks and 41 attacks in which either the onset or termination was indefinite were omitted. "Specific therapy" refers to treatment with anti-pneumococcus serum (horse or rabbit), sulfonamide drugs (sulfapyridine, sulfathiazole and sulfadiazine), or both. Of 48 patients who had no therapy in the first and specific therapy in the recurrence, nearly three-fifths had an attack of shorter duration in the recurrence than in the initial infection. This might be expected as the result of specific treatment. Among the patients who had the benefit of specific therapy during both attacks the duration of acute illness was the same in both initial and recurrent attacks in three-fifths of the cases. In the group who had no specific therapy in either attack more than 80 per cent of the recurrences were of the same duration or shorter than the initial attack. It would seem, therefore, that apart from the effect of specific treatment, the duration of acute illness in recurrences tends to be the same or shorter than in the first attack.

On the whole, the recurrent attacks were, therefore, less severe than the general run of pneumonias in this hospital as judged by the mortality, the incidence of bacteremia, and the duration of acute illness.

Frequency of recurrence as related to type of therapy. There is a suggestion in the recent literature that recurrences of pneumococcic pneumonia may be more frequent in patients treated with sulfonamide drugs in their first attacks than was the case with serum therapy. Hodes and his associates¹² treated 71 children with pneumococcic pneumonia with sulfapyridine and noted that four had a second attack within two weeks of the cessation of the therapy. In three of these the relapse was caused by the same organism as in the first attack. Davies,¹³ in a series of 154 cases in infants and children treated with sulfapyridine, had three recurrences at intervals of from 10 days to four months. In each case the same type of pneumococcus was found in successive attacks. Carey¹⁴ treated 387 infants and children with sulfapyridine or sulfathiazole alone, and 148 with the combination of specific serum and sulfonamides. None of the patients treated with combination therapy had recurrences within a year, but 11 of the patients treated originally with drug alone had a recurrence with the same type of pneumococcus from three to seven days after discharge from the hospital. Among adults, Dowling and Abernethy¹⁵ reported that six patients of 339 treated with sulfapyridine had recurrences after an interval of from nine to 25 days. Four were treated with sulfonamides alone and two with both serum and drugs. No case had the same type of pneumococcus in the recurrence as in the first attack. Hamburger and Rueggsegger¹⁶ reported a recurrence of Type I pneumonia two weeks after recovery from an initial attack of Type I pneumonia. Sulfapyridine was given both times. The patient had bacteremia in the first attack and empyema during the second.

These reports raise a number of questions in regard to the frequency and nature of recurrences of pneumococcic pneumonia in relation to chemo-

therapy (1) Is the incidence of recurrences different in adults and children? (2) Is the incidence of recurrences different when the initial attack is treated with serum or sulfonamides, or without either of these remedies? (3) Is there a greater tendency for recurrences with the same type of pneumococcus when the first attack is treated with drugs? (4) Is the interval between recurrences shorter in drug-treated patients? The factor of antibody response in relation to therapy will be considered in a subsequent section.

We have attempted to analyze our data with these questions in mind. Since all but one of the patients in this report were adults, no data are available with regard to the frequency of recurrences in children. Greene¹⁷ reported that 80 out of 561 children (18.2 per cent) had more than one attack of pneumonia. No bacteriological data were presented nor was specific therapy employed. In adults, it has been estimated that 15 to 20 per cent of patients with pneumonia have a history of a previous attack of the disease,^{1,18} but no series of cases with bacteriological data has been reported with an incidence as high as that. At present, it is impossible to say whether recurrences are more or less frequent in infants and children as compared with adults.

Since antipneumococcal serums have been employed extensively in this hospital for a number of years and sulfonamide therapy (exclusive of sulfanilamide) has been in use only two and a half years, the total number of recurrences in the two groups cannot be compared. We have, however, compared the frequency of recurrences *within two years* of an initial attack of pneumonia treated with specific serum, sulfonamide drugs, both serum and drugs, and no specific therapy.

In the past six years, in the Boston City Hospital, there were approximately 2000 untreated, non-fatal cases of pneumococcal pneumonia. During this period, 60 patients returned to the hospital with a second attack of pneumonia within two years of the first untreated attack. This is an incidence of 3.0 per cent. During the same period about 700 non-fatal cases of pneumonia were treated with specific antipneumococcal serum alone. Nineteen of these returned to the hospital with pneumonia within two years of the first attack—an incidence of 2.7 per cent. From October 1938 to June 1941 about 1200 non-fatal cases of pneumococcal pneumonia were treated with sulfapyridine, sulfathiazole or sulfadiazine alone. Of these, 18 or 1.5 per cent, treated with drug alone in the first attack, had a recurrence within two years. During the same period about 200 non-fatal cases were treated with both specific serum and sulfonamides, and six of these (3.0 per cent) had a recurrence of pneumonia within two years.

These figures are only approximate and by no means represent the actual incidence of recurrence of pneumonia within two years of the initial attack. All the patients who had recurrences did not necessarily return to this hospital. The estimates given lend no support to the idea that recurrences are more frequent with drug therapy than in untreated patients or in those

treated with specific serum. The incidence of recurrences in this series of adults is essentially similar to that reported in children by Davies, and Carey, and in adults by Dowling and Abernethy. Only Hodes reported a higher incidence (5.6 per cent) in children.

In the three series of cases in infants and children quoted above all but one of the drug-treated patients had the same pneumococcus type in the recurrence as in the initial attack. A summary of the data on this point in the present series of cases is given in table 7. Although the number of cases is small, there is a striking tendency for the drug-treated cases and the drug-plus-serum-treated cases to have the same type during initial and subsequent attacks. Further analysis of these cases, however, offers some explanation for these differences.

Of the 18 patients who had a recurrence within two years of a drug-treated first attack, seven had preexisting chronic pulmonary disease, and four of these had recurrences with the same type. Only one of the 19

TABLE VII
Relation of Therapy in First Attack to the Pneumococcus Type Found in Recurrences Within 2 Years

Therapy in First Attack	Recurrences within 2 Years		
	Total Number	Number with Same Type	Number with Different Type
No specific therapy	60	10	50
Serum	19	3	16
Sulfonamide drugs	18	10	8
Serum plus sulfonamides	6	3	3
Total	103	26	77

serum-treated cases, and 10 of the 60 patients who had no specific therapy during the first attack had chronic pulmonary disease. It is to be expected that recurrent attacks of pneumonia are more frequent in patients with chronic pulmonary disease, and 39 per cent of the drug-treated group fell into that category.

Two of the 10 drug-treated patients who had a recurrence with the same type had bacteremia in the first attack, two of the three patients who were treated with drug plus serum in the first attack and had a recurrence with the same type had bacteremia in the first attack. On the other hand, none of the group treated with serum alone, or treated non-specifically, who had recurrences with the same type had bacteremia in the first attack. Thus, the drug-treated group and the group treated with both drugs and serum had, on the whole, more severe initial attacks. It has been shown that focal purulent complications are more frequent in bacteremic than in non-bacteremic cases.¹¹ The chance for the persistence of pneumococci in foci in the lungs or elsewhere is probably greater in such cases.

The average interval between attacks in the drug-treated group was six months, in the drug-plus-serum-treated group 11 months, in the serum-treated group 17 months, and in the group without specific therapy, 11 months. It was shown (table 3) that the incidence of recurrence with the same type was greatest when the interval between attacks was less than six months.

When all factors are considered it seems likely that the greater tendency for recurrences to occur with the same type in both attacks in patients treated with drug alone in the first attack is to be explained on the basis of (1) a higher percentage of chronic pulmonary disease, (2) a higher incidence of bacteremia in the first attack, and (3) a shorter interval between attacks. The first two factors may be obviously chance occurrences in a small series of cases. However, the greater number of patients with chronic pulmonary disease among those treated with sulfonamide drugs may have resulted from the more frequent inclusion of such cases for treatment with drugs where previously they were not considered for specific treatment and, therefore, less often studied bacteriologically. The shorter interval between attacks in drug-treated cases would be of considerable significance if it should be substantiated by further observations on a larger number of cases.

Immunity reactions Antibody studies were done in a limited number of the patients who had two or more attacks of pneumonia. Only those with the same type of pneumococcus in each of successive attacks will be considered here. These patients may be grouped, according to type of treatment and the antibody response, into several categories.

(1) There were three patients who had serum treatment in the first attack with the development of antibodies, a recurrence with the same type of pneumococcus and no antibodies demonstrable on admission to the hospital at the time of the second attack. One had Type II pneumococcus in both attacks, and two had Type III. The shortest interval between attacks was 12 months. One of these patients had three attacks of Type III pneumonia and received serum after the second attack. The patient with Type II pneumonia had bacteremia in both attacks which were 12 months apart.

(2) Two patients received sulfonamide therapy in the first attack with the development of antibodies after crisis, and subsequently had a recurrence with the same type of pneumococcus and no antibodies demonstrable at the time of the second admission to the hospital. Both of these patients had Type III pneumonia in both initial and second attacks. The interval between attacks was six months in one case and 16 months in the other. One case had bacteremia in the first attack, neither case had bacteremia in the recurrent attacks.

(3) Two patients had homologous type-specific antibodies after crisis in the first attack which were still demonstrable at the time of the second admission and before the crisis in a recurrent attack which was associated

with the same pneumococcus type. One patient had Type I pneumonia for which she was treated with both serum and sulfapyridine, and homologous antibodies were demonstrated after the serum therapy. Six months later she suffered a recurrence of Type I pneumonia. Antibodies for Type I pneumococci were demonstrated in her blood serum on admission to the hospital 24 hours after onset of the second attack. She was treated with sulfathiazole in the second attack with prompt response. The organism in this case was "sulfonamide-fast" and the case has been reported previously.¹⁰ Another patient was treated for Type I pneumonia with sulfathiazole and sulfadiazine five months after recovery from an initial attack of Type I pneumonia treated with sulfathiazole. Antibody studies were not carried out during the first attack, but one day after the onset of the recurrence a high titer of antibodies for Type I was demonstrable. This patient had bacteremia during the first attack but not in the recurrence.

(4) Two patients failed to develop antibodies after recovery from the first attack and later had recurrences with the same type. One of these patients was treated with sulfadiazine during his first attack of Type I pneumonia. He responded rapidly to treatment, but developed no antibodies five days after crisis at which time he left the hospital. He returned four months later, again with Type I pneumonia, and again responded well to sulfadiazine therapy. No antibodies were demonstrable in the patient's serum at the time of the second admission, on the day of his crisis, nor during a period of three weeks after crisis. The other patient had both Types III and VIII in one attack of pneumonia during which no specific therapy was given. No antibodies for either III or VIII were demonstrable during convalescence from this attack. Four years later he had another attack of pneumonia with Type VIII pneumococcus.

(5) Four patients were treated with bivalent serum in the first attack and had recurrences with the second type which was not infecting the patient the first time, but for which antibodies were present in the antipneumococcal serum. The intervals between attacks varied from 21 months to eight years. One other patient had a recurrence with the same type (II) 21 months after receiving monovalent serum for Type II pneumonia. Antibody studies were not done in these five cases.

In summary, therefore, patients may have two or more attacks of pneumonia with the same type of pneumococcus, regardless of whether they are treated with serum, with sulfonamides or non-specifically during the first attack, and regardless of whether or not they develop antibodies for the homologous type after the first attack. Moreover, recurrences are noted despite the presence of homologous antibodies at the time of onset of the recurrence. Since all these combinations occur, it is impossible to correlate the immunity state with the likelihood of recurrence. Such correlation must await the accumulation of a larger body of data than is available at present.

COMMENT

In general, the conclusions reached in the earlier study of recurrences¹ have been confirmed in the present analysis of a considerably larger number of cases. As in the first study more than three-fourths of the cases had the same type of pulmonary lesion (lobar or atypical) in both the first and subsequent attacks. The conclusion that the various lobes are involved with the usual frequency in both attacks and that there is no correlation between the site of initial involvement and that of reinfection has been confirmed in the present study. In the present study bilateral involvement was no more frequent in recurrent attacks than it was in first attacks.

The inverse relation of the interval between attacks and the frequency of recurrence with the same type of pneumococcus in successive attacks is more evident in the present study with the larger number of cases. The frequency of occurrence of the various types of pneumococci in both initial and recurrent attacks was about what might be expected in a series of unselected cases of lobar and atypical pneumonia. The relatively frequent occurrence of Type III in successive attacks in the same patient may be explained by the known tendency of this organism to persist both in the healthy and in the convalescent carriers. As in the previous study, the bacteremic rate in the recurrent non-fatal cases was not greater than in the initial attacks nor was the mortality higher than would be expected in a series of unselected cases. In general, the initial attacks were of ordinary severity, as judged by bacteremia, multiple lobe involvement and age distribution, in comparison with non-fatal but otherwise unselected attacks of pneumonia. When the effect of treatment was taken into account, recurrent attacks were in the large majority of cases of the same duration or shorter than the initial attacks. A similar conclusion was drawn in the first study.

There is no evidence from this study that recurrences are more frequent among drug-treated patients than among those treated with serum or with no specific therapy. There was, however, a greater tendency for second attacks to recur at shorter intervals and for the same type to occur in both attacks than was observed in the cases treated with serum or with no specific therapy. This was only partially accounted for by certain chance factors such as a greater number of cases with chronic pulmonary disease and a higher bacteremic rate in this group of cases. The tendency for the disease to recur at shorter intervals and with the same type in drug-treated cases is suggested also from pediatric literature^{12, 13, 14} and in the report of Dowling and Abernethy¹⁵. It is difficult at present to assess the significance of this finding. It was evident from the previous study that the shorter the interval between attacks the more likely is the recurrence to be due to the same type of pneumococcus as the original attack. This is true regardless of the type of therapy employed in the first attack and is independent of any underlying chronic pulmonary disease. It may be related to persistence of the original infecting organism in the convalescent carrier state.

The rôle of immunity in relation to the tendency to recurrence of pneumonia is at present obscure. Evidence accumulated in this laboratory indicates that the antibody response of patients treated with sulfapyridine, sulfathiazole or sulfadiazine is no different from that observed in untreated patients who respond by spontaneous crisis^{20, 21}. Kneeland and Mulliken,^{22, 23} on the contrary, interpreted their findings as indicating a poorer antibody response in sulfapyridine treated cases. From the present data it would appear that any given case may or may not have a recurrence with the same type of pneumococcus irrespective of whether he develops antibodies after the first attack. At the time of the recurrence humoral antibodies may or may not be demonstrable. There is, of course no way to predict what immunity state will result following an attack of pneumonia or how long such immunity will persist.

SUMMARY AND CONCLUSIONS

A study of 168 patients with 191 recurrent attacks of pneumococcic pneumonia is presented. The initial and subsequent attacks did not differ significantly in the character or site of the pulmonary lesions, or in the distribution of the types of pneumococci involved. There was no increased tendency for recurrent attacks to be bilateral. Chronic pulmonary disease was a predisposing factor in only 15 per cent of the patients. In such patients, the attacks tended to recur at shorter intervals. The duration of the recurrent attacks was the same or shorter than the original infections. The frequency with which the same type was present in successive attacks was inversely proportional to the length of the interval between attacks. Type III was more frequently present in successive attacks than any other type. Successive attacks with the same type of pneumococcus were not more frequent in patients with chronic pulmonary disease than in other patients. Recurrences were not more frequent in patients treated with sulfonamide drugs in the first attack than in those treated with serum or in those treated non-specifically, but there was a tendency in the drug-treated cases for second attacks to occur with the same type and at shorter intervals. There is some indirect evidence that early recurrences with the same type of pneumococcus are associated with a persistence of the carrier state. There is no correlation between the antibody response and the tendency of pneumonia to recur.

REFERENCES

- 1 FINLAND, M., and WINKLER, A. W. Recurrences in pneumococcus pneumonia, *Am Jr Med Sci*, 1934, cxxxviii, 309.
- 2 COOPER, G., ROSENSTEIN, C., WALTER, A., and PEIZER, L. The further separation of types among the pneumococci hitherto included in group IV and the development of therapeutic antisera for these types, *Jr Exper Med*, 1932, lv, 531.
- 3 SABIN, A. B. Immediate pneumococcus typing from sputum by the Neufeld reaction, *Jr Am Med Assoc*, 1933, c, 1584.

- 4 CECIL, R L, BALDWIN, H S, and LARSEN, N P Lobar pneumonia A clinical and bacteriological study of two thousand typed cases, *Arch Int Med*, 1927, xl, 253
- 5 STILLMAN, E G A contribution to the epidemiology of lobar pneumonia, *Jr Exper Med*, 1916, xxiv, 651
- 6 CRUICKSHANK, R Pneumococcal infections II Lobar pneumonia in the community, *Lancet*, 1933, i, 621
- 7 FINLAND, M The significance of specific pneumococcus types in disease, including types IV to XXXII (Cooper), *ANN INT MED*, 1937, x, 1531
- 8 FINLAND, M, BROWN, J W, and BARNES, M W Immune reactions of carriers and non-carriers of type-specific pneumococci, *Am Jr Hyg*, 1940, xxxii, 24
- 9 FINLAND, M, and SUTLIFF, W D Infections with pneumococcus type III and type VIII, *Arch Int Med*, 1934, liii, 481
- 10 SOLOMON, S Chronic Friedlander infections of the lungs, *Jr Am Med Assoc*, 1940, cxv, 1527
- 11 TILGHMAN, R C, and FINLAND, M Clinical significance of bacteremia in pneumococcal pneumonia, *Arch Int Med*, 1937, lxx, 602
- 12 HODES, H L, STIFLER, W C, JR, WALKER, E, MCCARTY, M, and SHIRLEY, R G The use of sulfapyridine in primary pneumococcal pneumonia and in pneumococcal pneumonia associated with measles, *Jr Pediat*, 1939, xiv, 417
- 13 DAVIES, J A V The treatment of pneumococcal pneumonia in infants and children with sulfapyridine, *New England Jr Med*, 1939, ccxxi, 734
- 14 CAREY, B W The treatment of pneumonia in infants and children, *Jr Pediat*, 1941, xviii, 153
- 15 DOWLING, H F, and ABERNETHY, T J The causes of secondary fever in sulfapyridine-treated pneumonia, *ANN INT MED*, 1941, xiv, 1815
- 16 HAMBURGER, M, JR, and RUEGSEGER, J M Early recurrence of sulfapyridine-treated type I pneumococcal pneumonia, *New England Jr Med*, 1939, ccxxi, 445
- 17 GREENE, D Recurrence of pneumonia in infancy and in early childhood, *Am Jr Dis Child*, 1936, li, 284
- 18 WARR, O S, and ALPERIN, J Lobar pneumonia A report of 2039 cases, *ANN INT MED*, 1933, vi, 1474
- 19 LOWELL, F C, STRAUSS, E, and FINLAND, M Observations on the susceptibility of pneumococci to sulfapyridine, sulfathiazole, and sulfamethylthiazole, *ANN INT MED*, 1940, xiv, 1001
- 20 FINLAND, M, SPRING, W C, JR, and LOWELL, F C Immunological studies on patients with pneumococcal pneumonia treated with sulfapyridine, *Jr Clin Invest*, 1940, xiv, 179
- 21 FINLAND, M, STRAUSS, E, and PETERSON, O L Antibody response of patients with pneumococcal pneumonia treated with sulfadiazine and sulfathiazole, *ANN INT MED*, 1942, xvi, 1-16
- 22 KNEELAND, Y, and MULLIKEN, B Antibody formation in cases of lobar pneumonia treated with sulfapyridine, *Jr Clin Invest*, 1940, xiv, 307
- 23 *Idem* Antibody formation in cases of lobar pneumonia treated with sulfathiazole, *Ibid*, p 735

TREATMENT OF THE NEUROSES BY CLASS TECHNIC¹

By SAMUEL B. HADDEN, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

Group psychotherapy is not a new method of treating social and mental maladjustment. Those who were distressed of spirit and were comforted by Christ, Confucius and other great teachers were guided by their leaders in a way of life primarily through group instruction. All teachers are, in effect, psychotherapists who impart knowledge whereby men may attain to wisdom and live more happily.

Class technic has been used in the treatment of many varied disorders. My personal introduction to effective group psychotherapy was under the tutelage of Dr. Joseph Walsh at the White Haven Sanitarium. The remarkable alteration in outlook and the creation of hope that Dr. Walsh effected in men and women at White Haven were striking, but the effect upon the symptom of cough was even more remarkable. Dr. Walsh described the effect of coughing on the lesions of tuberculosis, and encouraged the patients to control the impulse to cough. Older patients reminded newer ones to exercise such control and gave helpful suggestions, this participation in the program of each other's improvement created a splendid morale, and it was actually unusual to hear a cough in a sanitarium for the treatment of tuberculosis¹.

Later, at the Philadelphia General Hospital I participated in group instruction of diabetics and of cases of neurosyphilis in the out-patient department. I soon found that it was extremely helpful to have new patients called aside in small groups and informed of the nature of their condition and given renewed hope through assurance that treatment would be efficacious. As a consequence, many who regarded themselves as doomed because of having been told they had syphilis of the brain soon became encouraged and cooperative. These experiences dictated my decision to utilize group psychotherapy in the routine handling of psychoneurotics at the Presbyterian Hospital.

At the present time the most successful exponents of group psychotherapy as a means of treating the neuroses are Pratt¹ of Boston and his co-workers, Harris² and Rhoades³. Their work has been carried on for 10 years or more. Many others, among them Lazell⁴ and Wender,⁵ have reported experiences with group psychotherapy in a variety of conditions.

About a year ago we began the use of the group technic in the neurological department of the Presbyterian Hospital as a means of economizing on the staff's time and effecting more satisfactory results than were obtained by

¹ Received for publication November 25, 1940.

From the Neurological Service of the Presbyterian Hospital, Philadelphia, Pennsylvania.

brief, individual interviews To this group were referred patients from the neurological and other dispensaries, patients whose complaints could not be demonstrated to have an organic basis and who were diagnosed as suffering from neuoses The only requirements for referral to the group have been that the patients be intelligent, understand English, manifest some degree of willingness to cooperate in treatment, have no particularly objectionable traits, and are not too far advanced to be incapable of reacting emotionally

The group has varied in size, with attendance ranging from six to 17 New members are admitted at any time during the year and are encouraged to continue, although about 20 per cent have dropped out An effort has been made to have at least one new member report each week, since this gives us the opportunity of repeating certain fundamentals weekly without the older members of the group being aware that such repetition is for their benefit

The setting of the classroom is decidedly informal, and no particular seating arrangement has been planned except that we have encouraged the older members and those who have received most benefit to take places in the front of the room This they are rather anxious to do The class usually opens by taking the roll of members, recognizing and commenting upon those who have been regular in attendance, and congratulating any returning backsliders The next few minutes are devoted to the new members, and a brief statement is made pointing out to them the reason for their being referred to the class As a rule, each of them has had a personal interview with the physician prior to admission to the group, but once again it is repeated they are being referred to the class because no evidence has been found that they are suffering from organic disease An explanation is given of how their varied symptoms are the result of transient alteration of function of various organs, brought about by disturbance of nerve impulses as a result of anxiety or other emotion Their attention is called to the sensations they may have experienced as a result of stage fright or other upsetting situations, and such sensations are compared to some of their symptoms As a rule, most of the patients complain of some cardio-respiratory or gastrointestinal disturbance, so the effect of emotion upon the functioning of the gastrointestinal tract and cardio-respiratory system is forcefully explained Veterans of the class are usually requested to tell in their own words how their emotions produced symptoms which at one time they were sure had been due to organic disease Such recitals generally make a decided impression upon the newcomers

After these brief and informal testimonials on the part of one or two members the effect of physical tension upon the nervous system is described The patients are informed that when they are physically tense the nervous system is made far more receptive to emotional or other stimuli They are then instructed in methods of relaxation They are asked to assume the

most comfortable position possible, with the feet placed firmly on the floor and the hands at the sides or crossed comfortably in their laps. They are then directed to focus their attention upon a simple object in the front of the room, and in a somewhat monotonous voice the leader describes how their attention is being narrowed down to a few suggestions and to the object before them. As attention is fixed their minds become more tranquil and they begin to experience a comfortable sensation of heaviness and drowsiness. This type of suggestion usually leads to effective relaxation of the majority of the members, and some few have drifted into snoring sleep. On some occasions, instead of focusing attention on a single object, they are requested to visualize a scene which the examiner describes. A soothing, pastoral scene is then depicted and the patients are asked to signal when they visualize it completely. When they are lulled into a tranquil state by suggestion, encouraging statements and suggestions are repeated, and the dynamics of some particularly common symptom is usually discussed. Later, patients experiencing the particular symptoms under discussion are asked for comment. The discussion continues informally in this vein. Very frequently hypothetical cases are outlined and the patients are asked to submit written comments on the cases described. Quite often the cases are those of members who are present, and the following week as their case is discussed such individuals frequently enter into the discussion with great vigor. They are often requested to outline a plan or course of action for themselves which is argued pro and con by the group.

During the course of each session inspirational bits of poetry are quoted or some helpful comments are made, and those who have favorite phrases or bits of philosophy are urged to contribute their little gems. In the early weeks of the class few were able to supply any particularly inspiring phrases or quotations, but after a few weeks of attendance all of them sought to contribute inspirational messages which they considered precious. By this and other means each patient is made to consider himself an important member of the group.

When the class was newly formed, as might be expected, most of the patients remained aloof while waiting for the session to begin. Later on a spirit of friendship and mutual interest grew up among them, and now they arrive at the hospital earlier each week in order to have more time to discuss various subjects which they have in common. They have found the group a new forum that in every way satisfies their gregarious instincts.

The importance of symptom production through conflict is impressed upon the minds of the patients. It is pointed out that conflict cannot exist in the presence of understanding. We try to make them appreciate their physical symptoms on a pathophysiological basis produced by emotion. During all lectures free use of examples and parables is made. Many of the individuals in the group have had at least some contact with the misinter-

preted psychoanalytic concept of mental illness and have great difficulty adjusting the biological and the social. The duality of the personality in this respect is discussed, and the necessity of repression and harmonious compromise is emphasized. Man's gregarious nature is a topic of free discussion, primitive desires and urges with their effect upon behavior are also subjects considered. The desirability of the dominance of intellectually directed behavior over purely emotional reactivity is stressed. Efforts are made to have patients recognize the effect of resentment, bitterness and other destructive mental forces in the production of symptoms and to develop resignation, charity and finer qualities in their stead.

Thus far the number of patients treated in our group has been too small to warrant any statistical report, but among those who have had greater experience Harris² reported in 1939 that 68 per cent of the patients treated showed improvement varying all the way from complete freedom from all symptoms to lessening of one or two complaints. In our small group several patients have reported remarkable improvement of gastrointestinal, cardiac and other visceral symptoms, with relief of pain, headache and depression being also frequently experienced. Up to this time only one patient has discontinued attendance at the clinics because of complete recovery. At present she is employed and cannot attend, but letters of greeting to the group and good wishes to the leader and individual members have been written on several occasions. This patient appears to have undergone a complete change of personality. Several others are coming to the class less frequently, one, regarding herself as entirely well but appreciating the inspiration the class affords her, admittedly is attending only to help out with the newcomers.

In an analysis of the effects it is interesting to examine the mechanisms that make improvement possible. Unquestionably, since all members are requested to supply a detailed written recital of their symptoms and personal history, the mechanism of catharsis is an important one. There has been definite evidence of the mechanism of transference, and there is no doubt that some element of rivalry for the attention of the leader has effected improvement. After a few sessions most of the patients begin to feel of some importance since their opinion is asked in discussion of the emotional difficulties of another member or hypothetical individual. Unconsciously they begin to apply some of the suggestions to themselves. There is little question that in the group "mob psychology" produces many of the results, and at certain of the sessions it has been apparent that a comment by a member is taken up by others and regarded as a gem of wisdom to which they promptly give allegiance and report benefit therefrom. It is interesting to note that when the group reconvened after a vacation of four weeks, they seemed to outdo each other in their desire to report great improvement.

SUMMARY AND CONCLUSION

The group method of treating the psychoneuroses is one that affords a partial solution of the problem of the psychoneurotic in the large urban hospital. The same technic and mechanisms that are applied to the management of the individual can be applied in dealing with the group. The organization of such classes for the management of the neuroses would, I feel, be an effective method of combating cults and quacks. With a little common sense and conviction any individual, regardless of personality, should be able to effect benefit through the group management of the psychoneuroses. I visualize the method as one that would be of great value in combating war neuroses.

REFERENCES

- 1 PRATT, JOSEPH H. The influence of emotions in the causation and cure of psychoneuroses, *Internat Clin*, 1934, iv, 1-16
- 2 HARRIS, HERBERT I. Efficient psychotherapy for the large outpatient clinic, *New England Jr Med*, 1939, ccxvi, 1-5
- 3 RHOADS, WILFRED. Group training in thought control for relieving nervous disorders, *Mental Hyg*, 1935, xiv, 373-386
- 4 LAZELL, E. W. The group psychic treatment of dementia praecox by lectures in mental reeducation, *U S Veterans Bureau Bull*, 1930, vi, 733
- 5 WENDLER, LOUIS. The dynamics of group psychotherapy and its application, *Jr Nerv and Ment Dis*, 1936, lxxvii, 54

THE RÔLE OF THE VERTEBRAL VEINS IN METASTATIC PROCESSES *

By OSCAR V. BATSON, M. A., M. D., *Philadelphia, Pennsylvania*

MILIARY tuberculosis, erysipelas, and tuberculous adenitis have lesion-patterns characteristic of diseases spread by blood and lymph vessels. These three diseases represent three types of spread. In miliary tuberculosis, the arterial blood stream distributes multiple foci at random. In erysipelas, organisms invade a plexus of lymph vessels and multiply. As a result the primary lesion enlarges, colony-like, from its margins. In tuberculous adenitis, the organisms spread in lymph vessels to multiply in the regional lymph nodes and lymph node chains. Modifications of the typical patterns are common. For example primary lesions in the left side of the heart, or in the lungs, may give rise to solitary, instead of multiple artery-borne secondary foci. An erysipelas-like lesion may appear atypical because of markedly irregular margins. A lymph gland chain may be only partially involved by disease and as a result the disease-pattern may appear discontinuous. These three lesion-patterns require only the classical, elementary concepts of a blood and a lymph system to explain their sequence.

Several diseases with primary and secondary lesions, particularly tumors, do not spread in the simple patterns noted above. The tumor metastatic patterns receive more attention than the patterns of infectious metastases, but the problem of spread of either sort of a metastasis is the same. The schema outlined above does not account for the high incidence of brain abscesses secondary to lung abscesses. If these brain abscesses develop from solitary, artery-borne emboli, why should the brain be so frequently the site of lodgment? The suggestion that the relation of the carotid arteries to the aortic arch is responsible for this frequency does not bear scrutiny—the secondary lesions occur in the brain only, not in other areas of the head supplied by the common carotid arteries. Carcinoma of the breast spreads to the other breast, to the ribs, to the vertebrae, or to any of these, and yet the lungs can remain free of disease. This non-involvement of the lungs is hard to explain if metastatic emboli must go from the breast to the right heart, to the lungs, and to the left heart before reaching the secondary foci noted above. Even an open foramen ovale has been called upon to explain this paradox. These "aberrant" metastases occur in as high as 40 per cent of cases¹. Lung capillaries too large to filter out cells in their passage through the pulmonary circulation have been suggested². Careful workers (Walther,³ Willis⁴) find microscopic carcinoma lesions in many lungs which might seem to indicate that no actual paradox exists. These interesting find-

* Read at the Boston meeting of the American College of Physicians, April 21, 1941.
From the Graduate School of Medicine, University of Pennsylvania

RÔLE OF VERTEBRAL VEINS IN METASTATIC PROCESSES

ings do not wholly clarify the problem. It is necessary to know whether these microscopic lung lesions preceded, occur concurrently or follow larger metastases. The microscopic size, suggesting a young lesion, indicate a tertiary lesion, i.e. one due to spread from a metastasis.

Handley⁷ devised the theory of permeation of the lymph vessels by tumor cell growth to explain the vagaries of spread of carcinoma of the breast. In brief, Handley's theory explains lesions at a distance by supposing an extensive erysipelas-type of a spread with the disappearance of the disease in the tissues between the primary and secondary sites. This theory is difficult to fit to a case of primary tumor in the left breast with a solid metastatic lesion as remote as the right frontal bone.

Prostatic carcinoma spread requires special consideration. The definitive diagnosis of primary prostatic carcinoma is frequently first made by the roentgenologist on finding metastases in the pelvis. The metastatic pattern is so characteristic as to warrant a positive diagnosis, is wholly unlike the peripheral lymph chain pattern. It seemed to me to resemble the vein plexus pattern. The spread of prostatic carcinoma cells through the pelvic veins would be in line with the recent trend of thought. Walther,⁸ Willis,⁹ and others, believe that carcinomas spread by the lymphatic system only so far as the regional lymph nodes—from there on the blood vascular system is the carrier.

The route of spread from the prostatic veins was studied by injections made in cadavers and in living monkeys. These and other vein injection studies have been reported in part (Batson⁶). In making the injections, advantage was taken of the fact that the deep dorsal vein of the penis is practically an integral part of the prostatic plexus of veins. (Figure 1)

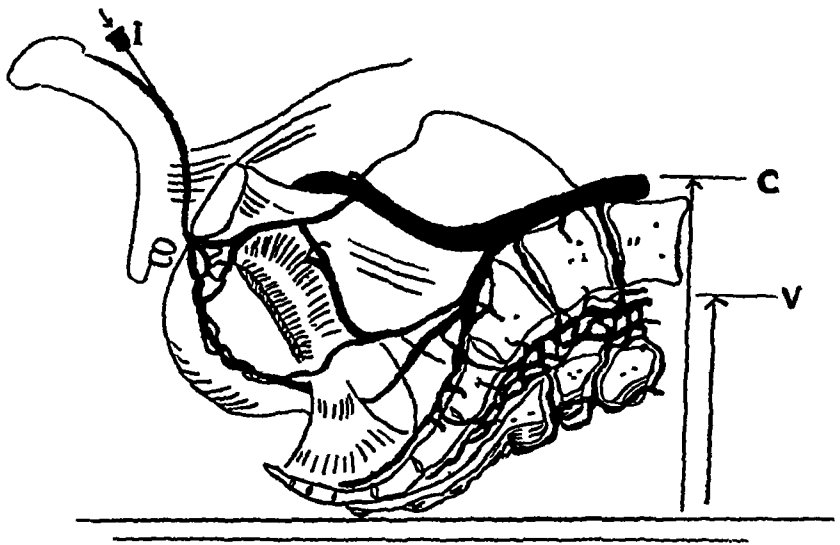


FIG 1 Diagram of the pelvic veins in a lateral view. *I*, the point of injection of the deep dorsal vein of the penis. Note the alternate routes by which the veins ascend the body. The difference between the height of the vena cava, *C*, and the vertebral vein plexus, *V*, is indicated by the arrows. This explains the ready filling of the vertebral plexus when the cadaver is in the dorsal recumbent position.

Injection of roentgen opaque substances into this vein in the cadaver was followed in roentgen films. A thin injection mass did not flow into the inferior vena cava but spread into the veins of the bones of the pelvic girdle and the veins in the vertebrae and those about the vertebral column, giving a replica of the spread of prostatic carcinoma. These are the veins first, and so well described by Breschet⁷ over 100 years ago. By adjusting the viscosity of the injection mass to the resistance of the vessels of various sizes the amount of injection mass to reach the inferior vena cava can be controlled. This is due to the fact that the vena cava is at a higher hydrostatic level than the vertebral veins, when the cadavers are in the dorsal recumbent posture (Figure 1). By increasing the quantity of mass injected the material reaches the brain. These experiments demonstrated a set of valveless, plexiform, longitudinal, venous channels that join the cranial venous sinuses to the pelvic veins without the intermediation of the lungs.

Injections of the living monkey indicated the probable sequence of events in the spread of metastases. Upon injection into the dorsal vein of the penis of the monkey the roentgen opaque material coursed to the inferior vena cava. This unquestionably is the normal course of flow in the living. When, however, the increased intra-abdominal pressure of straining was simulated by tying a towel around the monkey's abdomen, the injected material met resistance to passage through the vena cava and ascended the bone-protected vertebral vein plexus, and from there spread out into several intercostal vessels. This great network of veins around the spinal dura mater and the vertebrae serves as a venous pool or lake. It is of particular physiologic significance during the compression of the chest and abdomen in coughing, lifting, and straining.

The spread of injected material from the prostatic veins suggested the study of the spread from the breast veins. Here it was found that by the injection of a small breast venule in a cadaver the veins of the shoulder girdle, head of the humerus, thoracic vertebrae, neck, and brain were visualized in roentgenograms. The material, to be sure, also ran into the superior vena cava. Here was a pathway from another region to adjacent and remote parts, through a valveless network of veins that did not lead through the lungs. This network is a part of the same network that was filled by injecting the prostatic veins. It was suggested, therefore (Batson⁶), that all of the veins of the trunk wall, which would include the breast veins, all of the veins of the head and neck, the major *venae vasorum* of the vessels of the extremities, and the veins of the vertebral column (the vertebral veins, *sensu strictu*), be considered a separate vein system, to be called for brevity "the vertebral vein system." This vertebral vein system parallels the portal, the caval, and the pulmonary vein systems, providing a by-pass around these systems as well as serving as a venous pool during compression of the body cavities. This concept of a vertebral vein system clarifies many of the

"paradoxes" of metastatic spread, it does not supersede but rather complements concepts well founded upon obviously adequate evidence

I have had experience with over 100 anatomic injections, since the first report, summarized above. We now inject as an anatomic laboratory routine the deep dorsal vein of the penis of all male cadavers. Studies of the spread of material injected into the veins of the female breast have likewise been extended. Through the discussions of colleagues additional clinical applications have been brought out. This increased experience and the discussions permit additional comments to be made and some questions to be answered. Since the breast vein injections have been especially illuminating they will be described in detail.

In our routine cadaver injection we have used a colored latex emulsion. More recently a roentgen opaque medium has been added to this latex so that it is possible to follow the injection radiographically as well as visually. In the large number of cadavers that we have been able to observe, the variety and number of connections that exist between the caval system of veins and the vertebral vein system have become impressive. It is obvious that such valves as are present in the vertebral vein system are as a rule incompetent in later adult life. This has been previously noted by Franklin⁸ and others. In our routine injections of the deep dorsal vein of the penis we expect to obtain a fairly complete injection of the cerebral veins in 7 out of 10 cases. This is a very high proportion of successes for any routine injection technic and indicates the free communications present. Frequently the subpapillary venous plexus of the skin of the face is also injected (Figure 2).

The variety and number of connections between the caval and the vertebral vein systems are also to be noted during the course of a surgical laminectomy. The neuro-surgeon expects to see epidural veins fill and empty with each respiratory cycle. The slight changes in intra-thoracic pressure are sufficient to cause filling and emptying of the epidural veins through the multiple large connections. The total mass of vessels in the vertebral vein plexus becomes the more obvious the greater the number of injected anatomic specimens examined. It is assumed that any group of veins with a capacity for carrying more blood than the region requires is serving as a venous reservoir or lake. The vertebral vein system is therefore an enormous venous lake. It would appear possible for an embolus to remain for an indefinite period in this plexus of veins without being propelled into the heart. Regularity of direction of flow through a reservoir of this size is difficult to imagine. The direction must shift with each rise and fall of pressures at the communicating vessels, sometimes going toward the caval system of veins and sometimes longitudinally, either up or down. Solitary emboli, malignant or infectious, would likewise be propelled toward the heart or along the longitudinal extent. The same would be true for showers of emboli.

It has been objected, that according to this concept of spread, metastases

should invade the spinal cord as frequently as the brain. This sparing of the cord should be expected from the anatomy of the vertebral veins themselves. The small spinal cord veins pierce the dura and flow into the extradural plexus at right angles. The enormous main network of vertebral veins has in general a longitudinal course. These longitudinal vessels terminate cranially at the foramen magnum in the great venous dural sinuses. In brief the spinal cord is connected by small vessels to the vertebral vein plexus,



FIG 2 Photograph of the face of a cadaver after the injection of the deep dorsal vein of the penis. The injection by extending from the deep veins into the subpapillary plexus of the skin has produced the well marked mottling.

the cerebral venous dural sinuses are themselves the direct cranial continuation, in fact the terminus, of the vertebral vein system.

To this point we have considered the distribution of solitary and multiple emboli without the necessity of passage through the lung. The breast vein injections have suggested another type of spread by veins. To inject these breast veins it is necessary to use very small cannulae. A lachrymal cannula is most effective. Weber's water color vermilion, diluted to a watery

thinness, makes a good roentgen-opaque mass. India ink is satisfactory for visual observation. The injection of roentgen-opaque material is followed during injection with the fluoroscope. As much as 30 c.c. has been injected into the plexus of breast venules before the material was seen to flow into the intercostal or axillary vessels. While 30 c.c. is an unusual amount, 10 c.c. to 20 c.c. can commonly be injected into this sub-papillary venous plexus. These subcutaneous vessels are of more or less uniform size and exist in a branching and intercommunicating network. They are valveless. I have seen (figure 3) as small a quantity as 8 c.c. cause a suffusion of color into multiple areas of both breasts. No barrier exists at the midline. (Figure

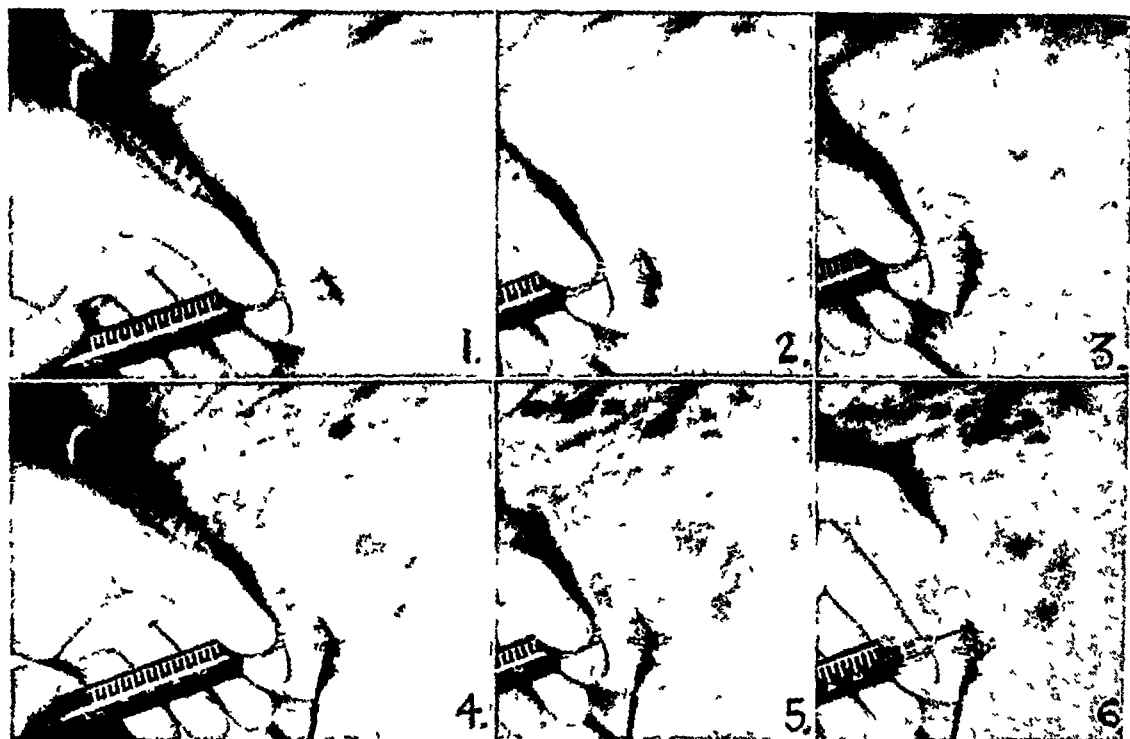


FIG 3 Six photographs from the motion picture record of the injection of a venule in the right breast of a female cadaver. Nos 1, 2, 3, and 4 show the injection of 8 c.c. of India ink. No 5 shows the effect of increasing the amount of injection and No 6 the specimen after the total of 24 c.c. had been injected. No resistance to injection was encountered.

4) These vessels are in sharp contrast to the lymphatic vessels with their small caliber and many valves. This venous network could be a route over which metastases spread, as well as the lymphatic plexus emphasized by Handley⁶. The entire pattern of the vein injection reminds one of *carcinoma en cunass*. Permeation of the subpapillary plexus of veins may be of greater importance than the permeation of lymphatics.

The anatomy of the veins, therefore, provides a mechanism for understanding both paradoxical emboli and skin permeation as in breast cancer. These concepts do not minimize the invasion of the lymphatics by carcinoma cells nor the direct spread along these lymphatic channels to the regional lymph nodes. The spread by veins, however, probably accounts for the very

rapid dissemination which can occur across the midline, for example, to the opposite breast

The technical difficulty of the demonstration of the central plexus of this vertebral vein system has delayed the appreciation of its rôle in the normal



FIG 4 Same cadaver as in figure 3. This view shows the extensive distribution of injected material to the opposite breast, the supraclavicular regions and the axillary fossa. The short vertical incisions on the left chest disclose the subcutaneous veins filled with the ink. The ink was also found in the cranial dura mater.

and pathologic economy of the body. Once the significance of these veins as a vein system is clear, many applications are possible. Hadden,⁹ for example, has noted the relationship of this vein system to the condition known as Spiller's ascending paralysis. Further, introduction of air into these veins

would account for the blindness and even death which sometimes follows the diagnostic perineal insufflation of air or air injections to produce pneumothorax. Taylor¹⁰ reports a case which he relates to the vertebral vein system. Several hours after an operation for empyema a woman patient collapsed and died. A careful autopsy disclosed an emboli in the large dural sinuses, none elsewhere, and no other significant findings. Taylor reasons that the air went from the empyema cavity into the azygous vessels and then by way of the vertebral vessels to the cerebral sinuses. Anoxia from the air emboli blocking the mouths of the Rolandic veins seems to have been the cause of death.

The ocular palsies accompanying incisional abscesses of the abdominal wall may depend upon emboli reaching the cranium through this system. The full significance of this venous route will be realized only when it is regularly examined at the autopsy table.

SUMMARY

The vertebral vein system consists of the epidural veins, the perivertebral veins, the veins of the thoraco-abdominal wall, the veins of the head and neck, and the veins of the walls of blood vessels of the extremities. It is a set of valveless vessels which carries blood under low pressures. In the subcutaneous tissue the smaller vessels provide a continuous network permitting ready permeation. Around the vertebral column the vascular bed of the system is much larger than required by the parts in which it is found. It is a system which is constantly subject to arrests and reversals in the direction of the flow of blood. The vertebral vein system parallels, connects with, and provides by-passes for, the portal, the pulmonary, and the caval systems of veins and hence can provide in itself a pathway for the spread of disease between remote organs.

BIBLIOGRAPHY

- 1 WILLIS, RUPERT A. The spread of tumors in the human body, 1934, J & A Churchill, London, p 321
- 2 WALTHER, HANS E. Untersuchungen über Krebsmetastasen, Ztschr f Krebsforsch, 1937, xlv, 313-333
- 3 WALTHER, HANS E. Der Nachweis sekundärer Knochengeschwülste, Radiol Clin, 1939, viii, 69
- 4 WILLIS, RUPERT A. Personal communication
- 5 HANDLEY, W S. Cancer of the breast and its treatment, 1922, London
- 6 BATSON, OSCAR V. The function of the vertebral veins and their role in the spread of metastases, Ann Surg, 1940, cxii, 138-149
- 7 BRESCHET, GILBERT. Recherches anatomiques, physiologiques et pathologiques sur le système veineux et voie anatomiques, 1832, Paris
- 8 FRANKLIN, KENNETH J. A monograph on veins, 1937, Charles C Thomas, Springfield, p 77
- 9 HADDEN, SAMUEL B. The rôle of increased intra-abdominal and intrathoracic pressure in the production of the demyelination and degeneration in the spinal cord, Presidential address, Philadelphia Neurological Society, February 1941
- 10 TAYLOR, STEPHEN. Spread of paradoxical metastases, Lancet, 1940, 638

A STUDY OF THE HEREDITARY NATURE OF GOUT; A REPORT OF TWO FAMILIES¹

By C J SMYTH, M D, and R H FREYBERG, M D,
Ann Arbor, Michigan

STIMULATED by the observation of gout in several members of one family we have made a systematic study of all of the immediate relatives of two gouty individuals in order to determine the importance of heredity as a factor in the etiology of this disease. In the vast amount of literature on the subject of gout and uric acid, reports of *proved* cases of gout in near relatives of patients in whom the diagnosis of gout has been established are sufficiently rare to make this study valuable. As far as can be determined, this is the first systematic investigation of the serum uric acid values in the immediate members of gouty families.

For many centuries it has been recognized that gout is very probably an hereditary disease. However, references to the subject usually contain only fragmentary data concerning the family histories. Scudamore,¹ in 1819, mentioned a butcher who could not trace gout to any former generation in his family but had three brothers who suffered greatly from the disease. This same writer observed a man with two sons and a daughter, out of five children, with severe gout, and another family of which the father, mother and all sons and daughters, four in number, had gout. He also noted confinement of this disease to only one or two members of large families. For example, out of 14 children only one brother and one sister had gout, in another family of 10 children with a gouty father only one son was afflicted. Garrod,² in 1931, observed a man who had his first "orthodox gout" in the great toe at the age of 20, his father, paternal grandfather, two brothers and three sisters all suffered from "true gout" and in a son of one of his sisters gout began at the age of 16 years.

It has been stated by many observers^{1, 2, 3, 4, 5, 6} that in from 50 to 60 per cent of all cases of gout there is a history of the disease in the parents or grandparents. These figures are based upon the patients' statements only and from the reports it appears that no attempt was made to verify the diagnosis by examining the relatives. Therefore, the accuracy of such statements is subject to considerable criticism. In the first place, it is well known that in gouty families the disease may skip several generations and, therefore, history of the malady occurring in ancestors may be elicited only by diligent inquiry, if at all. Very few people are able to give an exact

* Received for publication April 22, 1940

From the Rackham Arthritis Research Unit, the Medical School, University of Michigan, Ann Arbor

The Rackham Arthritis Research Unit is supported by the Horace H. Rackham School of Graduate Studies, of the University of Michigan

account of the ailments of their grandparents or great-grandparents. Furthermore, there can be little doubt that in the light of our present criteria for diagnosis many cases included in these early reports were probably diagnosed incorrectly. Many errors in diagnosis must have been made before modern laboratory methods for determination of blood uric acid concentration, and for proving the existence of tophi by chemical and histologic tests were available, and before diagnostic roentgenograms were employed. These early reports are valuable, therefore, only in that they suggest the hereditary tendency of the disease, they do not permit an accurate analysis nor do they indicate the mode of transference of the hereditary tendency.

The first study of blood uric acid values in an apparently healthy relative of a gouty patient known to us, is that of Folin and Lyman⁷ in 1913. They found an elevated blood uric acid value in a man "in whose family there had been more or less gout." This observation was apparently recounted subsequently (1915) by Folin and Denis⁸. The only other similar observations of which we are aware are contained in the more extensive report of Jacobson (1938)⁹. He found serum uric acid values definitely elevated in three "normal" males, all close relatives of three different gouty patients. Findings in other members of these families were not reported.

Garrod² has pointed out the need for studies of the uric acid concentration of the blood of members of gouty families from infancy upwards in order accurately to evaluate the importance of heredity in this disease.

METHOD

In this investigation we have studied each immediate member of the families of two gouty patients, a total of 29 individuals. Besides attempting to detect the presence or absence of gout by history and physical examination, in all of the adults serum uric acid content was determined. Venous blood, obtained in practically all instances after a 12 hour fast, was immediately placed under oil, allowed to clot, and the serum analyzed by the indirect method of Folin¹⁰. By this method normal individuals have serum uric acid values of less than 6 mg per cent so that values greater than this have been considered abnormally high. In many cases diagnostic roentgenograms of joints were made.

REPORT OF FAMILY I

The genealogy of the first family investigated is illustrated in chart 1. The presence of gout has been established in the father and his three sons. The only members not completely studied are related by marriage or are children under five years of age. We were very anxious to determine uric acid content in these children but were unable to gain permission for this. None of these children have had joint symptoms.

The serum uric acid values are shown in table 1. In the figures indicated by the asterisk the values are not during a fasting state.

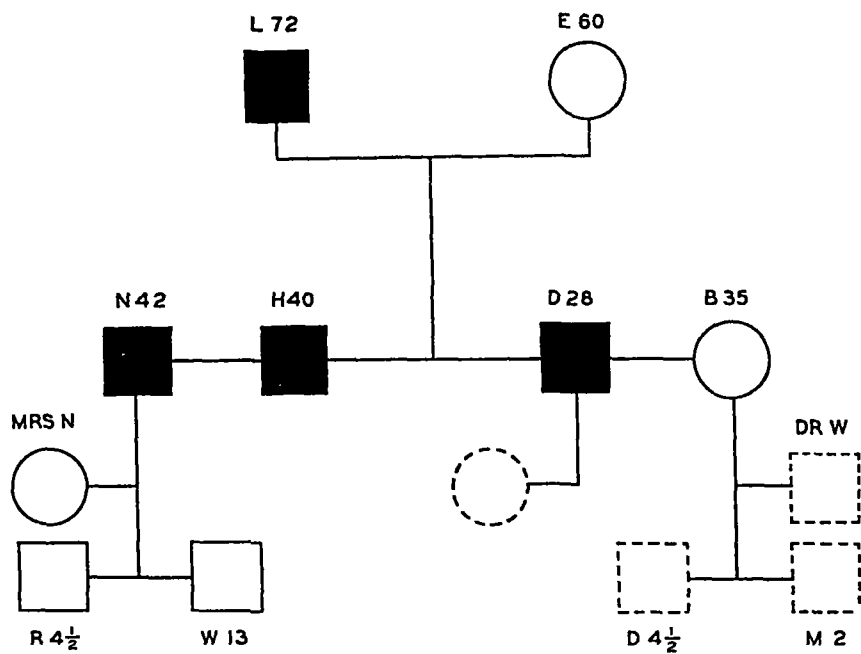


CHART I An analysis of Family I The squares represent males and circles, females Proved cases of gout are shown in black The letters signify the name and the numbers, the age of each member The dotted squares and circles represent members without uric acid studies

TABLE I
Serum uric acid values in members of Family I, in all cases determined during fasting state except where indicated by asterisk

	Date	Serum Uric Acid mg per cent
L W (Father)	10/16/39	7 9
	10/12/39	8 08
	12/16/39	9 2
E W (Mother)	10/12/39	6 06
	12/16/39	5 3
H W (Son)	9/19/39	8 89
	9/22/39	9 8
	10/ 6/39	10 0
	12/16/39	7 6
N W (Son)	10/12/39	11 43
	11/11/39	9 8
	11/28/39	9 8
D W (Son)	1/19/40	*10 2
B W (Daughter)	1/19/40	*5 7
N W , Mrs (Daughter-in-law)	11/11/39	3 87
W W (Grandson)	10/12/39	4 70
R W (Grandson)	10/12/39	4 44

Case histories of the four men, in whom the diagnosis of gout has been made, follow

Case 1 L W (father), aged 72 years, Jewish, machinist At the age of 42 years for the first time he had a sudden attack of severe pain accompanied by signs of inflammation sharply localized about each great toe He was confined to bed for five weeks Recovery was complete without any residual abnormality Six months later, without any apparent cause, another similar attack occurred Since that time he has had repeated bouts of joint pain, usually located in the feet and most marked in the region of the metatarsophalangeal joint of the great toes During each attack all of the characteristic signs of acute inflammation develop The duration of each attack has varied from a number of hours to three weeks Hot packs and salicylates usually gave temporary and only moderate relief During the past 10 years the attacks have occurred more frequently, about one each month, and no longer completely subside during the last two years he has had pain almost constantly in the shoulders, right second metacarpophalangeal joint, knees, and ankles For several years he has noticed small chalk-like deposits in both ears These occasionally ulcerate and from them a granular, gritty material exudes

His father lived to the age of 80 years and to the patient's knowledge, had never been troubled with joint disease He did not know anything about his grandfather, aunts or uncles He has one living sister, seven years his senior, who has never had any joint symptoms

Physical Examination There were typical tophi in the ears (figure 1) One



FIG 1 Right ear of L W, father of Family I, showing small ulcerated tophus from which sodium urate crystals were demonstrated

tophus on the right ear was ulcerated and from this crystals of sodium urate were demonstrated, the murexide test was positive The right first metatarsophalangeal joint was slightly swollen, tender, and painful and in it motion was moderately reduced The right second metacarpophalangeal joint was slightly swollen and tender

Laboratory Data The fasting serum uric acid value was repeatedly elevated (table 1) Sugar was found in two of three urine samples examined By the Shaffer-Somogyi method the fasting blood sugar was found to be 116.5 mg per cent, which we consider slightly elevated A tophus was removed by taking a wedge-shaped section from the left ear, and sections prepared according to the method of De Galantha¹¹ contained sodium urate crystals Roentgenograms of the feet showed extensive changes in many joints, large cystic and punched out areas characteristic of the late stages of gout were present (figure 2)

Diagnoses Typical tophaceous gout, questionable diabetes mellitus

Case 2 N W (son), aged 42 years, married, came to the Arthritis Unit at our request. His chief complaint was attacks of multiple joint pains which he had had for 13 years. Early in the course of the disease the attacks occurred only every two or three years, in recent years, however, they occurred about every four months, and they persisted considerably longer than in the early stages of the disease. The attacks begin suddenly with extreme pain shortly followed by swelling, redness and increased heat, and were most often located at the metatarsophalangeal joint of the right great toe. The ankles, knees, and elbows have been similarly affected. These bouts of pain occurred most frequently in the fall and spring and were not related to exposure or over-indulgence in food and alcoholic drink. Various forms of therapy



FIG 2 Roentgenograms of L W, father, Family I, showing multiple punched out juxta-articular lesions in toes

had been instituted, including fever induced by "fever cabinet" and injections of sulfur. During the first attack only he took colchicine in whiskey which gave almost immediate relief.

Physical Examination The only abnormality was slight tenderness over the right first metatarsophalangeal joint.

Laboratory Data Repeated fasting serum uric acid values were elevated (table 1). The erythrocyte sedimentation rate was 0.95 mm per minute (Ernstene-Rourke method). Roentgenograms of both feet showed small rounded areas of rarefaction along the proximal phalanx of the right great toe, and along the lateral margin of the head of the right first metatarsal bone (figure 3).

Diagnosis Chronic gout

He was advised to eat a low-purine diet, and when last seen had been asymptomatic for three months

Case 3 H W (son), aged 40 years, single, was the first member of this family studied. He had had repeated attacks of pain in the ankles and right great toe for 10 years. Each attack began suddenly and the pain was so severe that weight bearing was impossible. Slightest pressure over the affected joints produced almost unbearable discomfort. At first these bouts of pain occurred once a year but they became more frequent and during the last two years he has had six attacks. They frequently follow sharp decreases in environmental temperature. Each episode has lasted from one to seven days. Although early in the course of the disease he was entirely free of symptoms between attacks, during the last three months he had almost constant aching pain in the ankles and has had occasional pains in the left wrist unaccompanied

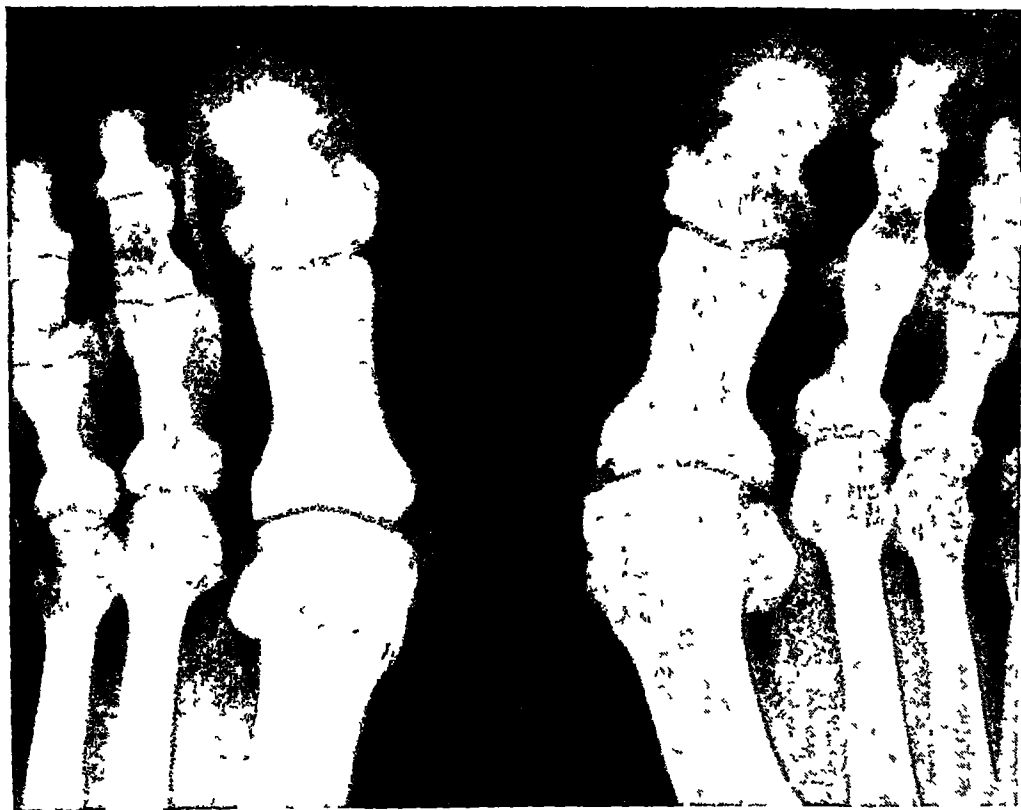


FIG 3 Roentgenograms of N W, son, Family I, showing punched out juxta-articular areas at the metatarso-phalangeal joints of each great toe

by evidence of inflammation. Through his cooperation all other immediate members of this family have been studied.

Physical Examination Entirely negative

Laboratory Data Numerous uric acid values were significantly elevated (table 1). Two urinalyses showed no abnormalities and the hemoglobin and complete blood counts were normal. The erythrocyte sedimentation rate on two occasions was 0.40 mm per minute (Ernstene-Rourke method). Roentgenograms of the ankles, feet and wrists showed only slight changes.

Diagnosis Pre-tophaceous gout

An attempt was made to induce an attack of gouty arthritis by the use of a high fat diet according to the plan suggested by Lockie and Hubbard¹². A diet com-

posed of 50 gm of protein, 160 gm of fat, and 45 gm of carbohydrate was eaten for two weeks, during which time no increase in joint symptoms occurred, in fact, the ankle pain almost completely disappeared. Since this time he has been eating a low-purine diet and has been free of symptoms.

Case 4 D W (son), aged 28 years, married. This person was visited in his home, and he reported that he had had one attack of severe *podagra* during each of the last five years. Each attack had a sudden onset of pain, soon followed by all of the signs of acute inflammation. The shortest attack had been two days and the longest 11 days. He had had no symptoms for five months. No tophi were found and the joints showed no physical abnormalities. His physician informed us that he had examined the patient during one of his attacks and considered it to be typical of gout. A non-fasting serum uric acid value was 10.2 mg per 100 c.c. (table 1).

Diagnosis Pie-tophaceous gout.

The other members of this family who have been examined show no positive evidence of gout. In the case of E (mother) the first serum uric acid value obtained was 6.06 mg per cent (borderline); the second determination revealed a value of 5.3 mg per cent. The blood non-protein nitrogen content at this time was 35 mg per 100 c.c. The only daughter in this family had no history of joint disease, her serum uric acid value was 5.7 mg per cent (non-fasting). The two grandsons who were examined exhibited no evidence of gout.

REPORT OF FAMILY II

The father of this family has chronic gout. Two sons have significantly elevated serum uric acid values, another son has a high normal value, and the only daughter has an average normal value (table 2). None of these children have had symptoms of gout at any time. We were unable to obtain blood for uric acid analysis from any of the grandchildren, all of whom are under five years of age. The genealogy of this family appears in chart 2.

TABLE II

Serum uric acid values in members of Family II, in all cases determined during fasting state except where indicated by asterisk.

	Date	Serum Uric Acid mg per cent
F B (Father)	11/27/39	7.27
	11/14/39	7.02
	11/14/39	8.60
N B (Mother)	11/27/39	3.69
R B (Son)	11/16/39	7.94
D B (Son)	11/27/39	8.42
C B (Son)	11/27/39	5.60
G B (Daughter)	1/19/40	*4.3

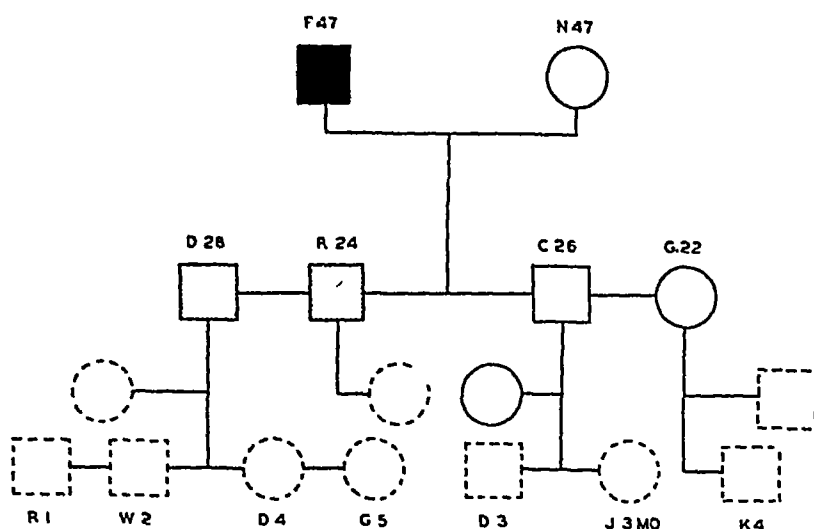


CHART II An analysis of Family II. The squares represent males and circles, females. The solid black square indicates the existence of proved gout. The shaded squares indicate members with significantly elevated serum uric acid values. The letters and numbers signify the name and age of each member. The dotted squares and circles represent persons without uric acid studies.

The case history of the father follows.

F W., aged 47 years, steel mill worker, was able to recall the exact date of his first attack of joint pain—October 27, 1933—when sudden sharp pain developed in the right great toe. He was unable to walk for five weeks. The attack completely subsided without residual deformity or tenderness. One year later a similar attack occurred in the same joint and, in addition, the right ankle was similarly affected. With each attack the involved joints have been greatly swollen, red, and hot and at that time even the slightest pressure caused almost unbearable pain. Two years after the initial episode another attack occurred which lasted five weeks and which was similar to the first two. In May, 1939, the fourth attack occurred, which affected the right shoulder and knee, the left elbow, wrist and hand, in addition to the right great toe and ankle. Soreness persisted in all of these joints throughout the summer and fall of 1939 and an acute exacerbation occurred three weeks before his admission to this hospital, November 15, 1939.

Physical Examination He was moderately overweight, apparently comfortable and could bear his full weight on both feet. No tophi were found. The left wrist was swollen, tender, painful and moderately limited in motion. The skin over the dorsum of the left hand and wrist was moderately cyanotic. The right knee was slightly swollen and contained an increased amount of synovial fluid. The right great toe was slightly tender at the metatarsophalangeal articulation.

Laboratory Data Repeated serum uric acid determinations have on each occasion shown high values (table 2). Synovial fluid and blood serum removed simultaneously contained 8.6 and 8.4 mg of uric acid per 100 c.c. of fluid respectively, and each fluid contained the same (low) amount of vitamin C, i.e., 0.34 mg per cent (Farmer-Abt method, 1935). The erythrocyte sedimentation rate was 10 mm per minute. There was a small erosion of the head of the left first metatarsal bone shown in the roentgenogram (figure 4).

Diagnosis Chronic gout.

He was given colchicine 0.0005 gram (1/120 grain) hourly for eight hours and following the fourth dose there was a marked improvement in his symptoms. After

two days slight stiffness of the left wrist was the only abnormal physical finding. He was instructed to eat a low-purine diet and discharged from the hospital. When seen five months later he reported that he had had no joint symptoms during this interval.

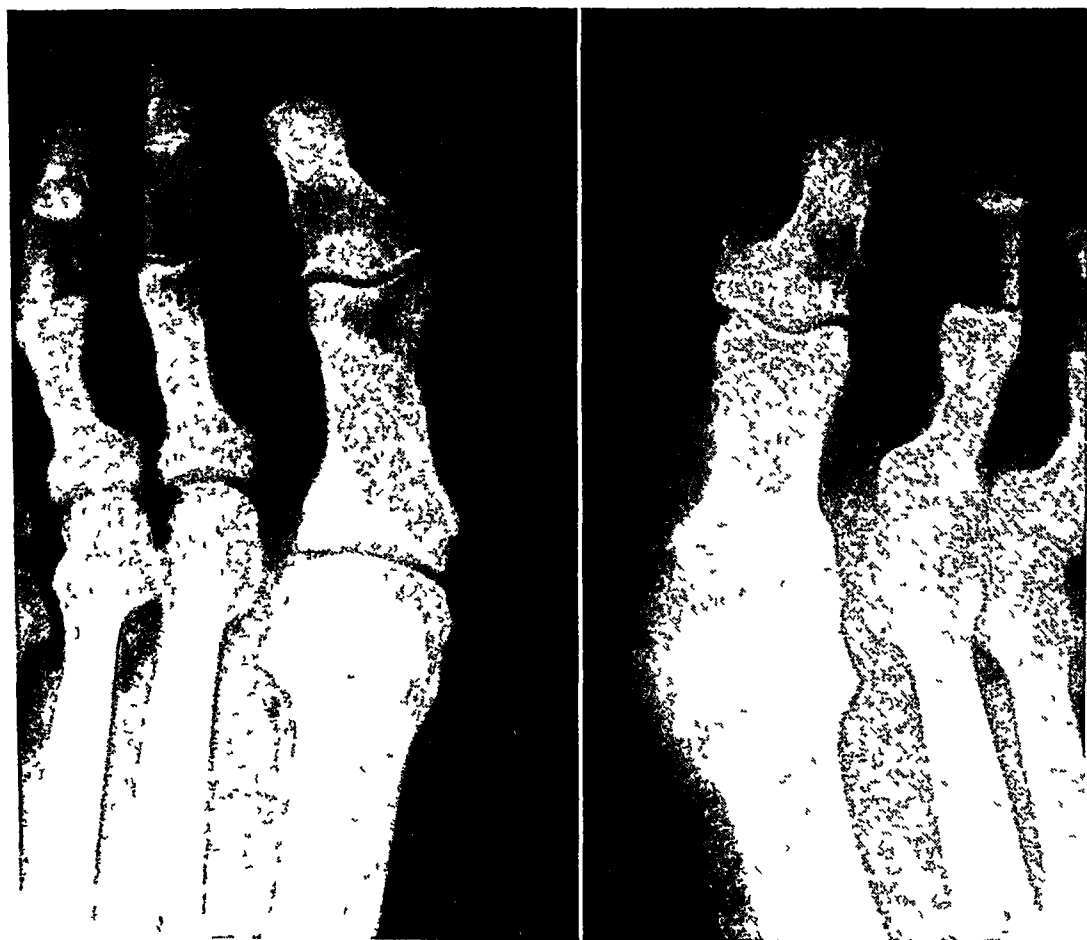


FIG 4 Roentgenograms of F B, father, Family II, showing a small area of erosion at the head of the left first metatarsal bone

DISCUSSION

In the two families that form the basis of this report all but one of the adult male members (eight) have gout or have elevated serum uric acid values, whereas all of the adult female members (four) have had no symptoms of gout and no hyperuricemia. These findings are in agreement with many other reports that this disease occurs primarily in males. At present there is no adequate explanation for the disproportionate occurrence in males, but this fact suggests that gout may be transmitted as a sex-linked hereditary factor. However, in another disease *known* to be hereditary with sex-linked transmission, i.e., hemophilia, only alternate generations suffer from the disease even though members of both sexes of the unaffected generation transmit the hereditary tendency of the disease. Our data show that gout exists in successive generations, which is strong evidence against its being transmitted as a sex-linked character.

It has been suggested by Bauer, Fischer, and Lenz¹³ and by Gairod² that the predisposition to gout is inherited as a simple dominant character and is transmitted according to Mendel's laws. If this be true, one would expect the disease to appear in *every* generation since it is impossible for a dominant factor to be present in the germ-cell and its effect not be manifested. The fact that in gouty families the disease may skip one or two generations and then reappear requires explanation if gout is transmitted as a dominant mendelian factor. Gairod² explains this by suggesting that persons inherit the susceptibility to gout which in itself is not detrimental to its host but under the influence of certain external factors not yet completely understood, such as trauma, fatigue, diet, and exposure, the disease becomes manifested. This theory has not yet been proved.

Because gouty individuals so frequently have abnormally high blood uric acid concentration and abnormal urinary excretion of uric acid, the disease is considered to be dependent upon an error in purine metabolism. The exact metabolic fault is not known, however, nor is the true significance of the hyperuricemia understood. Although other diseases may cause high blood uric acid values, the occurrence of hyperuricemia in children and close relatives of gouty individuals, in the absence of renal insufficiency and liver disease, logically appears to indicate the existence of the metabolic abnormality responsible for, or characteristic of, gout. Further study of the blood uric acid content in relatives of gouty patients will undoubtedly clarify this, and by such a study the relationship of the metabolic fault to the clinical manifestations of gout may become evident, as will the mode of transference of this apparent inborn error of metabolism. We shall watch with great interest the course of events in the sons, D and R, of Family II of this report. If in later years they show clinical evidence of gout, it will be apparent that the present hyperuricemia indicates the existence of the metabolic fault prior to gouty attacks. Further, should they or others with high blood uric acid values but without clinical manifestations of gout have children with hyperuricemia and gouty attacks, Gairod's theory of transmission of a "susceptibility" to gout would have scientific support.

This study indicates the importance of investigating the relatives of gouty patients for the presence of gout. By such an investigation in Family I of this report the existence of gout was established *for the first time* in the father and two brothers of the original patient (H). If, whenever the diagnosis of gout is made, all close relatives of the patient are carefully studied, many persons might be found to have gout at a much earlier time than would be the case in the ordinary course of events, and proper management of such individuals would eliminate much unnecessary suffering and incapacitation.

The findings in the families, herein reported, suggest that there is an important hereditary factor in the etiology of gout. We believe that the hereditary aspects of this disease have not been sufficiently recognized. However, whether or not *all* cases of gout are truly hereditary, or whether

the disease may be acquired, requires much further study. Further, the exact mode of transmission of an hereditary factor cannot now be stated, primarily because too few families have been carefully investigated. It is our hope that this report will stimulate further studies of similar nature so that the exact importance of heredity in relation to this disease might be understood.

SUMMARY

The families of two gouty individuals have been systematically studied. Each member was questioned and examined for evidence of gout, in most cases blood was quantitatively analyzed for uric acid, and in some instances joints were studied roentgenographically. Seven of the eight adult male members of these two families have hyperuricemia and five have clinical gout. In one family the father and all three sons have gout, in the other family a gouty father has two sons who have definite hyperuricemia but no other manifestation of gout. None of the females in these two families have any evidence of this disease. Case histories of the five men with gout are presented.

This study indicates the importance of investigating relatives of gouty patients for the presence of this disease. Some of the problems of the hereditary nature of gout are discussed.

BIBLIOGRAPHY

- 1 SCUDAMORE, C. A treatise on the nature and cure of gout and rheumatism, 1819, Edward Earle, Philadelphia.
- 2 GARROD, A. E. The inborn factors in disease, 1931, Oxford Press, New York.
- 3 GARROD, A. B. The nature and treatment of gout and rheumatic gout, 1859, Walton and Maberly, London.
- 4 ALLBUTT, T. C. Gout, in *The Oxford Medicine*, 1936, IV, pt. 1, chap. IV, 82, Oxford University Press, New York.
- 5 WEIL, M. P. L'hérédité des goutteux, *Presse méd.*, 1934, xlii, 701-702.
- 6 PRATT, J. H. Gout, in *Nelson Loose-Leaf Med.*, 1923, III, chap. 3, 37, Thomas Nelson and Sons, New York.
- 7 FOLIN, O., and LYMAN, H. On the influence of phenylquinolin carbonic acid (atophan) on uric acid elimination, *Jr Pharmacol. and Exper. Therap.*, 1913, iv, 539-546.
- 8 FOLIN, O., and DENIS, W. The diagnostic value of uric acid determination in blood, *Arch. Int. Med.*, 1915, xvi, 33-37.
- 9 JACOBSON, B. M. Uric acid in serum of gouty and non-gouty individuals: its determination by Folin's recent method and its significance in diagnosis of gout, *Ann. Int. Med.*, 1938, xi, 1277-1295.
- 10 FOLIN, O. Standardized methods for determination of uric acid in unlaked blood and in urine, *Jr Biol. Chem.*, 1933, ci, 111-125.
- 11 DE GALANTHA, E. Technic for preservation and microscopic demonstration of nodules in gout, *Am. Jr. Clin. Path.*, 1935, v, 165-166.
- 12 LOCKIE, L. M., and HUNNARD, R. S. Gout: changes in symptoms and purine metabolism produced by high fat diets in 4 gouty patients, *Jr. Am. Med. Assoc.*, 1935, civ, 2072-2075.
- 13 BAUER, E., FISCHER, E., and LEVY, F. *Human Heredity*, translated by Eden and Ceder Paul from the Third German edition, 1931, The Macmillan Company, New York.

CHEMOTHERAPY OF PNEUMONIAS AND IMMUNITY REACTIONS *

By IRVING M. BULLOWA, M.D., F.A.C.P., NATHAN H. SHACKMAN, M.D.,
and DANIEL STATS, M.D., *New York City*

In the selection and application of our available resources for the treatment of pneumonias, we should be guided by consideration of the interaction of pneumococci and patients and the effect of our remedies on both. Final judgment must be based on clinical experience with adequately sized similar groups of patients treated with various therapies. Patients who completely recover from pneumonia without benefit of specific therapies do so by reason of their immunity response which completely destroys the invading bacteria, and such patients as a rule exhibit acquired immunity to the invading organism. Accordingly, the capacity to overcome infection, which is a cardinal characteristic of patients, must be considered when we compare the effect of different treatments.

The Effects of Therapy. Chemotherapy with sulfonamides, specific serum therapy, or a combination of both, are current methods of successful treatment. Serum therapy passively augments the specific immunity response. The effect of chemotherapy on the pneumococci and on the development of immunity deserves attention.

Therapeutically, the sulfonamides affect the pneumococci by killing them or depressing their vitality so that they produce less capsular carbohydrate. The capsular carbohydrate is that portion of the pneumococcus which gives pneumococci their specific character and their virulence or capacity to produce disease. In figure 1 (the graph) which is from work done in our laboratory with a standardized strain of pneumococcus III observed for growth with and without exposure to 5 mg per cent sulfapyridine, it may be seen that the effect of the drug was not immediately noticed and the decrease in colonies did not occur until four hours had elapsed. After 26 hours the organisms escaped from the effect of sulfapyridine and the colonies increased in number. Much more carbohydrate was present in the control culture than in the one exposed to sulfapyridine. If a sufficient amount of an effective drug is in contact with the pneumococci for a sufficient time, all of them are killed (bactericidal action). All the organisms do not die at the

* Read before the Sections on Practice of Medicine and Pharmacology, Annual Session of the American Medical Association in Cleveland, Ohio, June, 1941. (Presented in part as the first William H. Friedman Lecture, Denver, Colorado, on Feb. 20, 1939.)

Received for publication July 25, 1941.

From the Medical Service, Harlem Hospital, Department of Hospitals, New York City, N. Y., and the Littauer Pneumonia Research Fund of New York University College of Medicine. These studies received additional support from the Metropolitan Life Insurance Company, and from Mr. Bernard M. Baruch, Mr. Bernard M. Baruch, Jr., Miss Belle N. Baruch, and Mrs. H. Robert Samstag.

Constance Lebar assisted in the statistical analysis.

same time and if the concentration is insufficient or the pneumococci are too numerous and resistant, only some are killed and the others are temporarily held in check (bacteriostatic action) After medication is discontinued these dormant organisms may become active again unless sufficient antibodies develop or are supplied

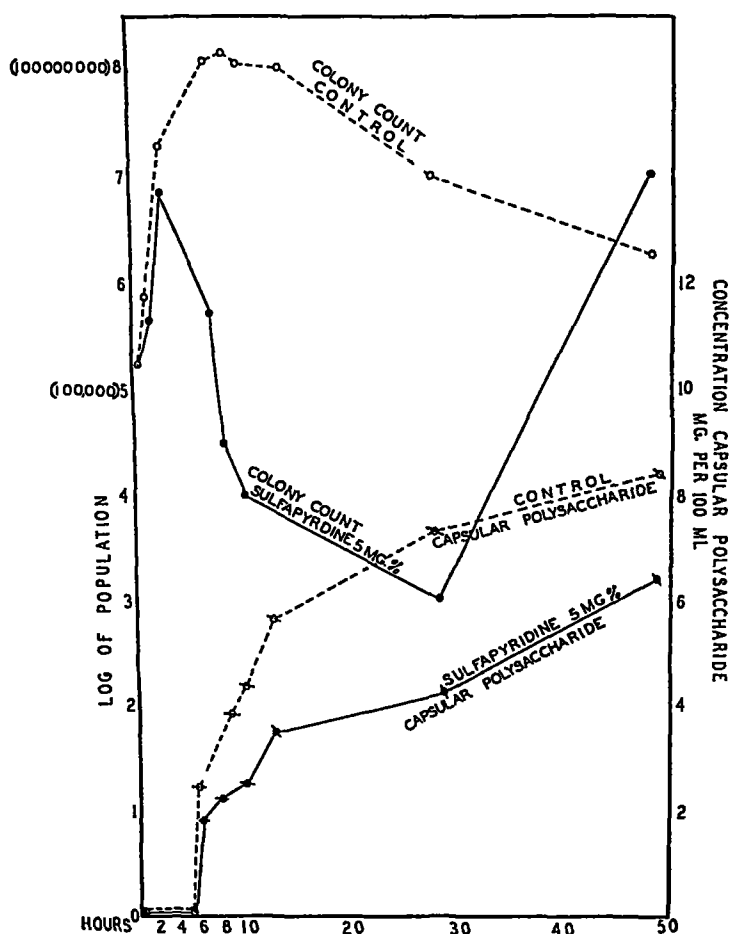


FIG 1 Curves of growth and production of capsular polysaccharide with and without sulfapyridine *Pneumococcus III* In the presence of 5 mg per cent sulfapyridine growth was unaffected for four hours After the fourth hour there were fewer organisms than in the control The number of organisms diminished until the twenty-sixth hour when their multiplication was accelerated so that at the forty-eighth hour there were even more organisms in the culture with sulfapyridine than in the control The production of capsular substance in the presence of sulfapyridine was less than in the control

The patient (figure 2) whose chart is shown was treated with sulfadiazine and a concentration was obtained sufficient to sterilize the blood and lower the temperature and permit development of antibodies Only a very small amount of antibody was detectable for a single day All the organisms were not destroyed—there was a reinvasion of the blood with a fatal outcome

The Selection and Administration The most effective sulfonamide drug is one which acts upon the organism causing the illness, penetrates the

CHEMOTHERAPY OF PNEUMONIAS AND IMMUNITY REACTIONS

tissues, and maintains a high concentration of free drug with little to action. It should be administered early in the disease while the organisms are few in number, the initial dose should be large so as to achieve promptly a high concentration, and further doses should be repeated sufficiently often to maintain the desirable concentration uninterruptedly for the shortest necessary period. The organisms are then all destroyed or so weakened that they do not overwhelm the immunity mechanism and there is less likelihood of toxic action which depends, in part, upon the amount of drug given.

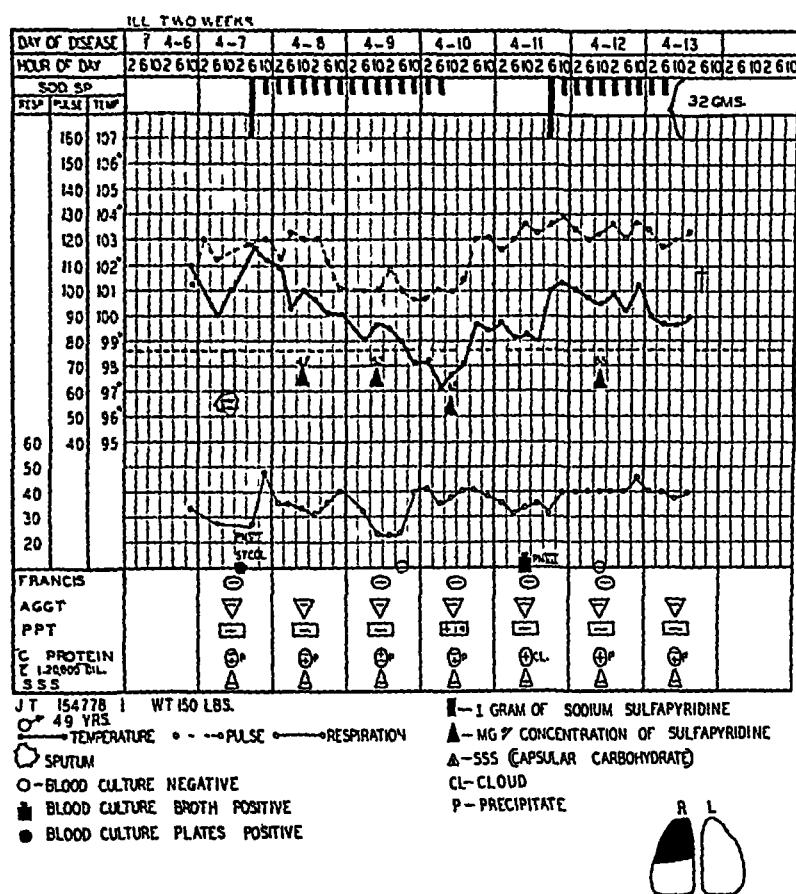


FIG 2 49-year-old man whose pneumococcus VII bacteremia was temporarily controlled with sulfapyridine. The chemotherapy was discontinued when the temperature was 97° F. Acute phase protein was present and on a single day there was a very small amount of precipitin. The organisms had not been completely destroyed by the drug or by the immunity mechanism.

A male patient (figure 3), 36 years old, was treated with sulfapyridine on the second day of his illness for a pneumococcus IV pneumonia of the left lower lobe. A high concentration was found, a total of only 18 grams of the drug was used and, on the tenth day, agglutinins were demonstrable. It will be noted that the drug was effective in the concentration obtained and the immunity mechanism was activated.

The absolute effectiveness of a sulfonamide drug upon pneumococcus

DAY OF DISEASE	1		2		3		4		5		6		7		8		9		10		11		12		13		14			
HOUR OF DAY	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10
SP																														
PESP	PULSE TEMP																													
160																														
150																														
140																														
130																														
120																														
110																														
100																														
90																														
80																														
70																														
60																														
50																														
40																														
30																														
20																														
10																														
FRANCIS																														
AGCT																														
PPT																														
PROTEIN																														
C _r 2.5 GRS																														
S S S																														
R.B. 155254 WT 180 LBS.																														
♂ 36 YRS																														
—TEMPERATURE • —PULSE —RESPIRATION																														
○ SPUTUM																														
O-BLOOD CULTURE NEGATIVE																														
■ - 1 GRAM OF ENSEALS SULFAPYRIDINE																														
▲ - MG / CONCENTRATION OF SULFAPYRIDINE																														
▽ - SSS (CAPSULAR CARBOHYDRATE)																														
CL - CLOUD																														
P - PRECIPITATE																														

Leukocytosis and Leukopenia Usually in response to pneumococcic infection there is a granulocytic leukocytosis which disappears when immunity develops either spontaneously or in response to therapy. When sulfonamide drugs are given the fall of the white blood count occurs with fall of pulse and temperature, as a result of the effective action of the drug. However, when the sulfonamide drugs are given for a long time, or to sus-

ceptible individuals, the migration of white blood cells may be depressed and an agranulocytic leukopenia may develop. Furthermore, leukopenia in which the per cent of granulocytes is not depressed may occur, due to the toxic action of pneumococci. In this last type of case the administration of sulfonamide drugs does not depress the count but causes it to rise. In these patients, though the white blood count is low, the bone marrow is active. When there is an agranulocytic leukopenia due to disease or other phenol-

RESPONSES TO PNEUMOCOCCI

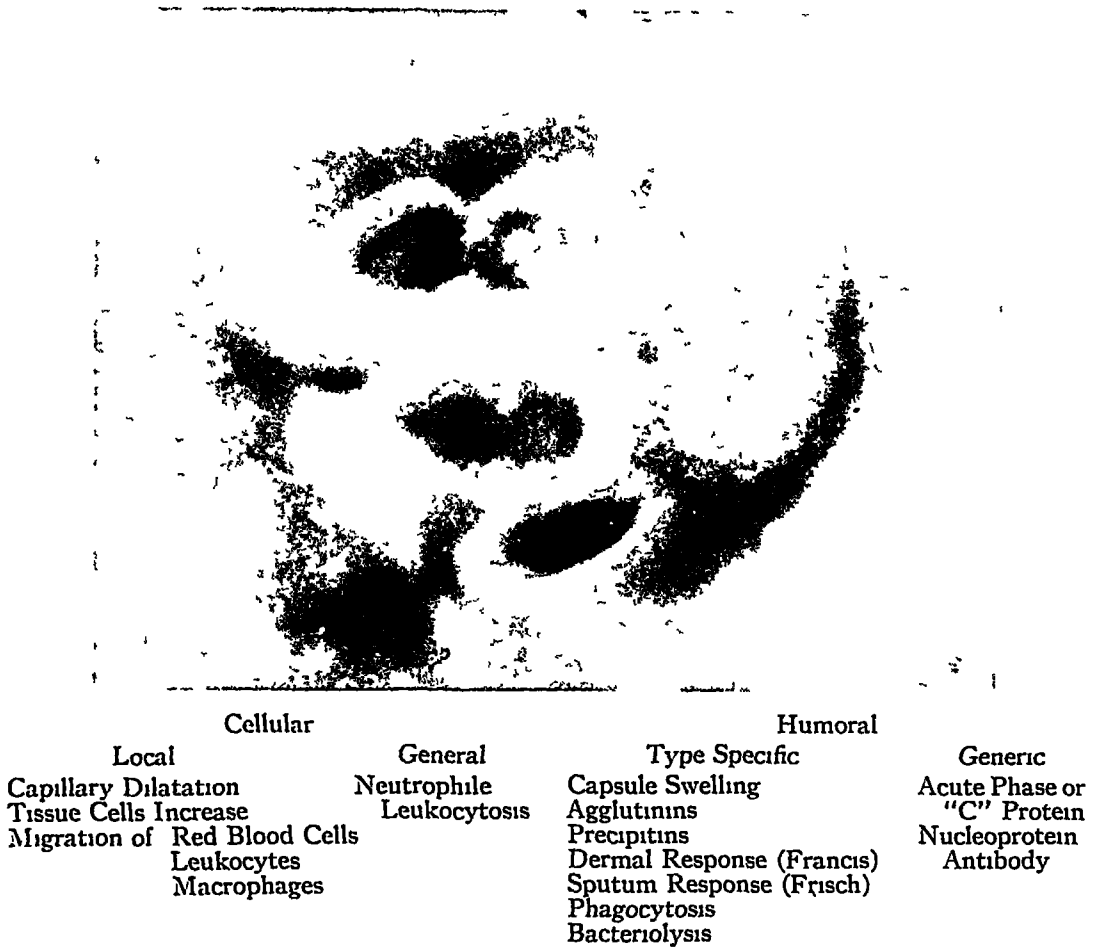


FIG 4 Electron-microscopic photograph of pneumococci

containing drugs, an additional insult to the bone marrow with sulfonamides may be hazardous. The migration of leukocytes into infected cavities may be halted by the sulfonamides so that empyema pus fails to thicken and purulent infiltration of the meninges is lessened. The density of consolidation may be less. This chemotactic depression or counter action of leukocyte migration may prove advantageous.

Complement Whether recovery from pneumonia requires active complement to be present is still unknown, but if it is required it would be

desirable to determine whether complement activity is impaired by sulfonamide administration. The hemolytic complement was studied in a human system and found unaffected in normal persons and in pneumonia patients to whom sulfonamide drugs had been administered in the usual way.

Capsular carbohydrate induces the production of type specific antibodies. These antibodies precipitate capsular carbohydrate (thereby limiting edema in the lungs), and swell the capsules of pneumococci and agglutinate them, and at the time of crisis, by sensitizing them, assist in both lysis and phagocytosis. These processes may be observed in the sputum, as pointed out by Frisch². The carbohydrate produces little if any harm in the absence of pneumococci which otherwise consist largely of nucleoprotein. We have observed carbohydrate continuously present for months in the blood of a patient with spondylitis due to pneumococcus III.

To a degree, the virulence of a pneumococcus is determined by the amount and character of the *capsular carbohydrate* produced and its ability with pneumococci to act as an antigen or induce the production of antibodies. In some cases the carbohydrate is detected in the blood and in the urine or in an infected serous cavity. The significance of detecting capsular carbohydrate in the blood was investigated. The patients were being rotated for treatment with serum therapy, chemotherapy and the combination. These studies covered two periods. In the first period, from November 20, 1939 until February 18, 1940 the study was confined to infections with pneumococci of types I, II, III, IV, V, VII and VIII. The results have already been reported³. Another series was studied from July 1, 1940 to May 1, 1941. The series differ because the latter study was made over a longer time including periods of lesser virulence of pneumonia and the cases were studied much less intensively than the earlier cases. Capsular carbohydrate was detected in the blood of 6.6 per cent of the combined groups (see figure 5). It was not found in the blood of 97 type I patients, 51 type IV patients or 16 type V patients. It occurred most frequently in type III patients with an incidence of 13.5 per cent of patients. In the first series it had been present in 27.5 per cent of the pneumococcus III patients. It was found in three of the 33 type II, in five of the 101 type VII, and in six of the 65 type VIII patients. The death rate in the patients with detectable capsular carbohydrate was 58.1 per cent (18 deaths among 31 patients). It was only 12 per cent in the cases without carbohydrate, 53 among 458 patients. When there was neither bacteremia nor capsular carbohydrate present (figure 6) our death rate, regardless of kind of treatment, was 7.5 per cent and when there was a bacteremia present without any capsular carbohydrate the death rate was 35 per cent. The death rate in patients who had capsular carbohydrate without bacteremia was 60 per cent, and with both bacteremia and capsular carbohydrate 56.2 per cent. The detectable specific carbohydrate occurred about five times more frequently in patients over 40 years of age than in those younger and twice as frequently after the fourth day of disease than in those coming for treatment earlier.

SSS INCIDENCE

(CAPSULAR CARBOHYDRATE)

MORTALITY RATES

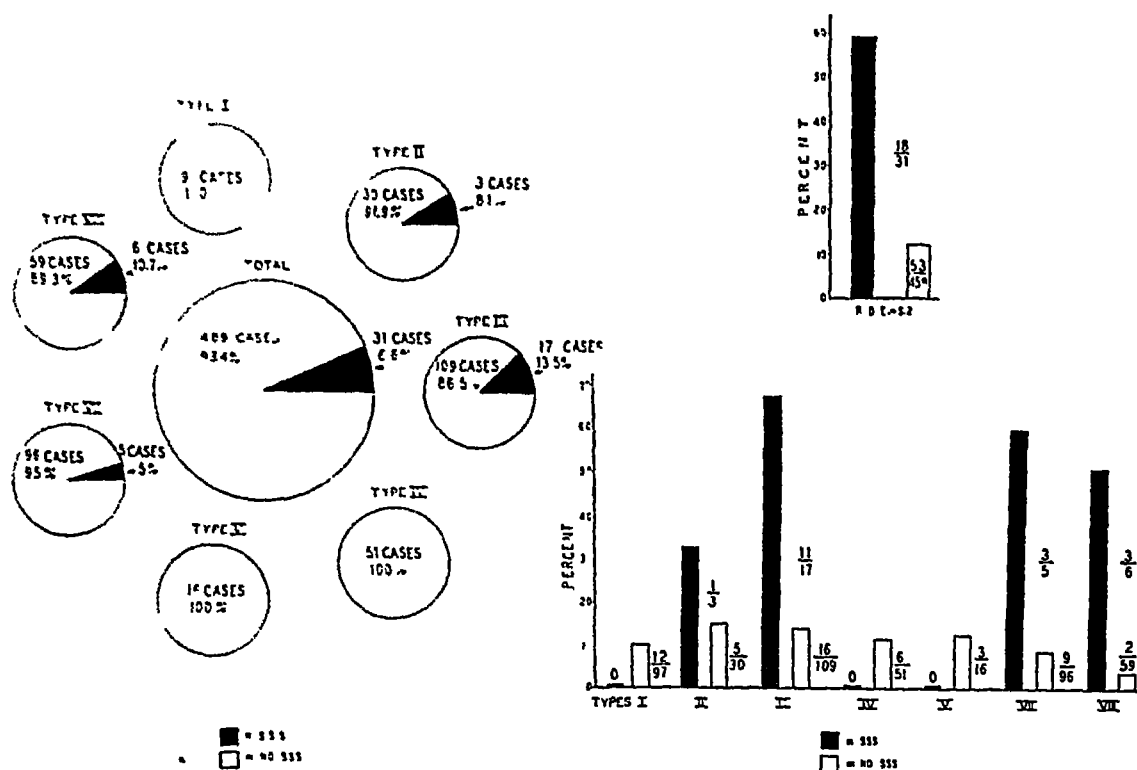


FIG 5 Pneumococcus I, II, III, IV, V, VII, VIII pneumonias, Nov 20, 1939-Feb 18, 1940 and July 1, 1940-May 1, 1941 Capsular carbohydrate (SSS) incidence in two series of pneumococcal pneumonias combined and by types and the influence of its detectable presence on mortality combined and by types

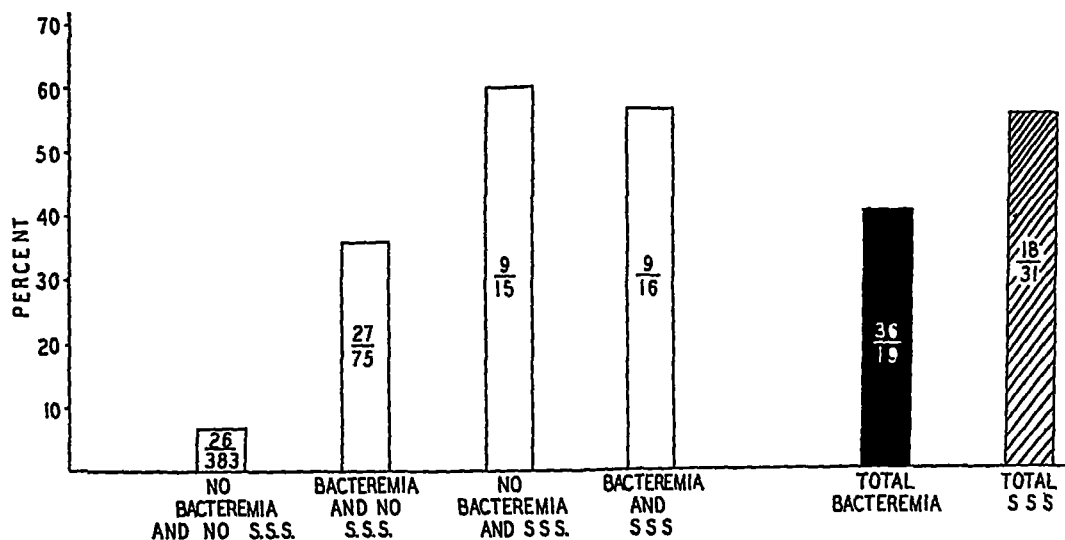


FIG 6 Mortality rates of Pn I, II, III, IV, V, VII, VIII pneumonias in relation to detectability of SSS and bacteremia, Nov 5, 1939-Feb 18, 1940 and July 1, 1940-May 1, 1941

Specific antibodies (agglutinins and precipitins) appeared in 66 per cent of the 88 patients treated with chemotherapy of the types included in the analyses (figure 7) Antibodies developed least frequently in the pneumococcus III patients and most frequently in those infected with pneumococcus VII Almost two-thirds of the pneumococcus I, three-fourths of the pneumococcus II, one-half of the pneumococcus III, two-thirds of the pneumococcus IV, 57 per cent of the pneumococcus V and 70 per cent of pneumococcus VIII patients developed antibodies Antibodies were more frequently detected in patients under 40 years of age than in those above 40, i e , in 72 5

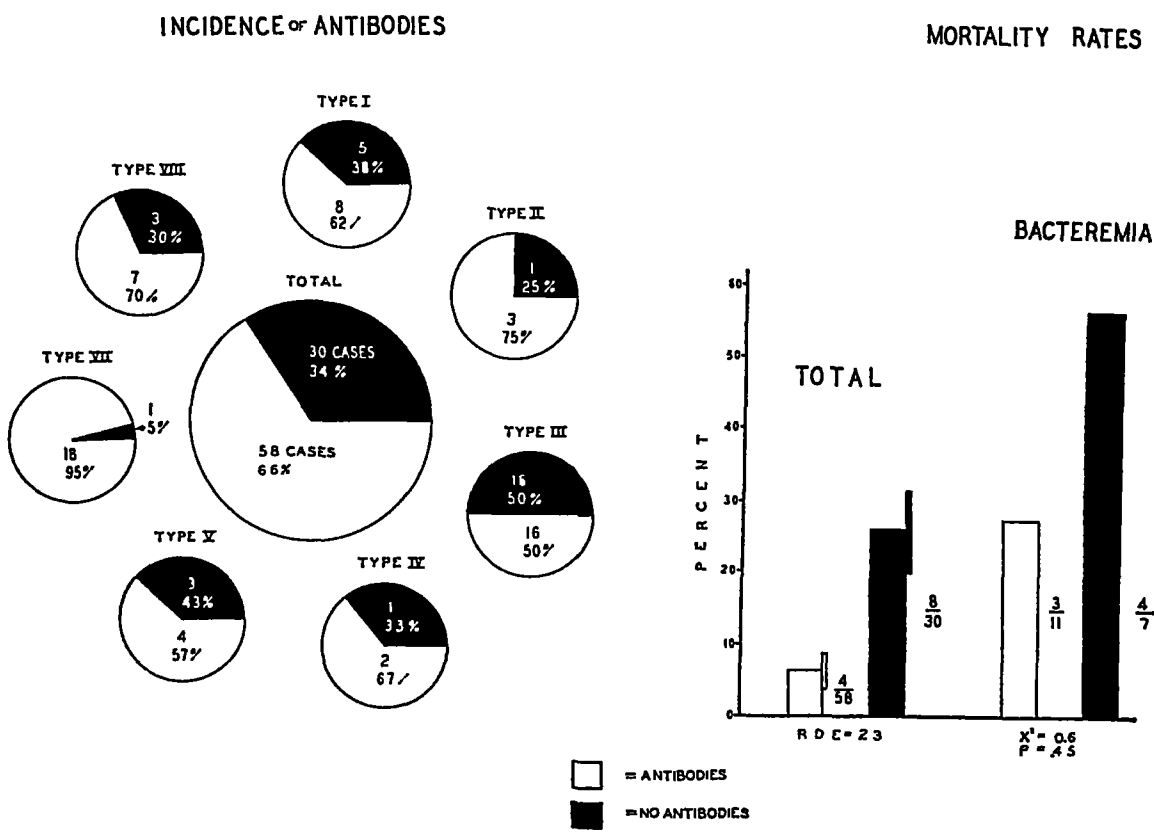


FIG 7 Pneumococcus I, II, III, IV, V, VII, VIII, pneumonias—chemotherapy Nov 20, 1939–Feb 18, 1940 and July 1, 1940–May 1, 1941 Incidence of antibody development in certain pneumococcal pneumonias given chemotherapy, and the influence of the presence of antibody on mortality in all the patients and also in those with bacteremia

per cent of those under 40 and 60 per cent of those over 40 In the older patients there was a higher mortality rate, the patients who did not develop antibodies had a mortality almost four times greater than those who did develop them The death rate in the patients who developed antibodies under 40 years of age was 3 5 per cent Those who did not develop antibodies in that age group had a death rate of 9 1 per cent In those over 40 the death rate was 10 3 per cent when antibodies appeared, and when they were absent it was 36 9 per cent Of the cases treated early, only one of the 22 who developed antibodies died (5 per cent) Three of the 36 patients

treated after the fourth day who developed antibodies died (83 per cent) Eighty per cent of 58 patients, in whom the exact time of onset was known and who received chemotherapy, did not develop antibodies until after the eighth day None of the patients who developed immunity before the eighth day died The importance of immunity development was exemplified in a 29-year-old pneumococcus III patient (figure 8) who was treated with sulfadiazine on the seventh day of his illness On admission and until the

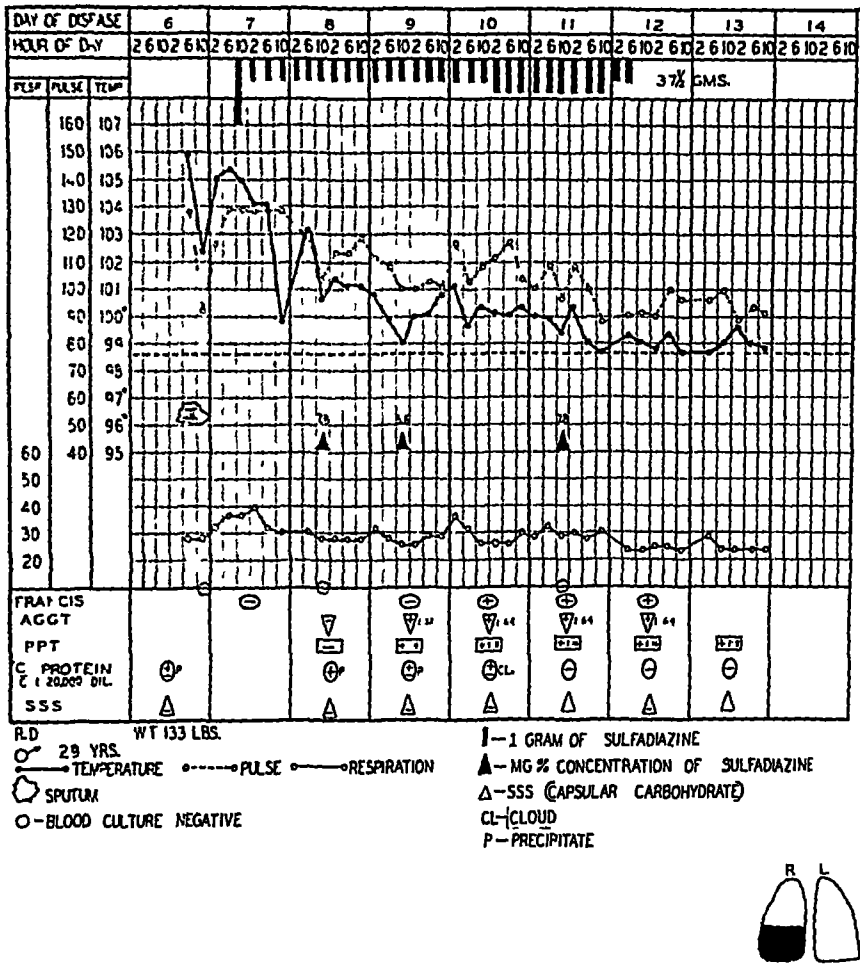


FIG 8 A 29-year-old man who was treated with sulfadiazine on the seventh day developed immunity on the ninth day Treatment was continued until the twelfth day This was probably longer than necessary There was no reason to continue the drug longer

ninth day there was no evidence of protective immunity On this day his temperature was normal but the pulse was accelerated On the ninth day also there was a faint immunity response This increased on the tenth day and the Francis test became positive as well Because the drug concentration had been low and the temperature and pulse were elevated, increased dosage was given There was firm immunity, "C" protein disappeared on the eleventh day, and the drug was stopped

A separate analysis of 12 pneumonia patients (figure 9) treated with sulfapyridine or sulfadiazine revealed that the skin test with type-specific polysaccharide became positive in 25 per cent of the cases on the sixth to tenth day of the disease without relation to temperature fall. Two of these three patients also developed agglutinins and precipitins in their blood. Only one patient in the group died. He failed to develop a positive skin test, precipitins were faintly demonstrable on only one occasion. The drug was prematurely discontinued (figure 2). Of the eight recovered patients who failed to develop a positive dermal reaction, four developed precipitins as well as agglutinins and one developed precipitins only.

Acute Phase Protein ('C' Protein) In addition to the specific carbohydrate which is in the capsule of the pneumococcus and which stimulates the production of specific antibodies, there may be extracted from the bodies

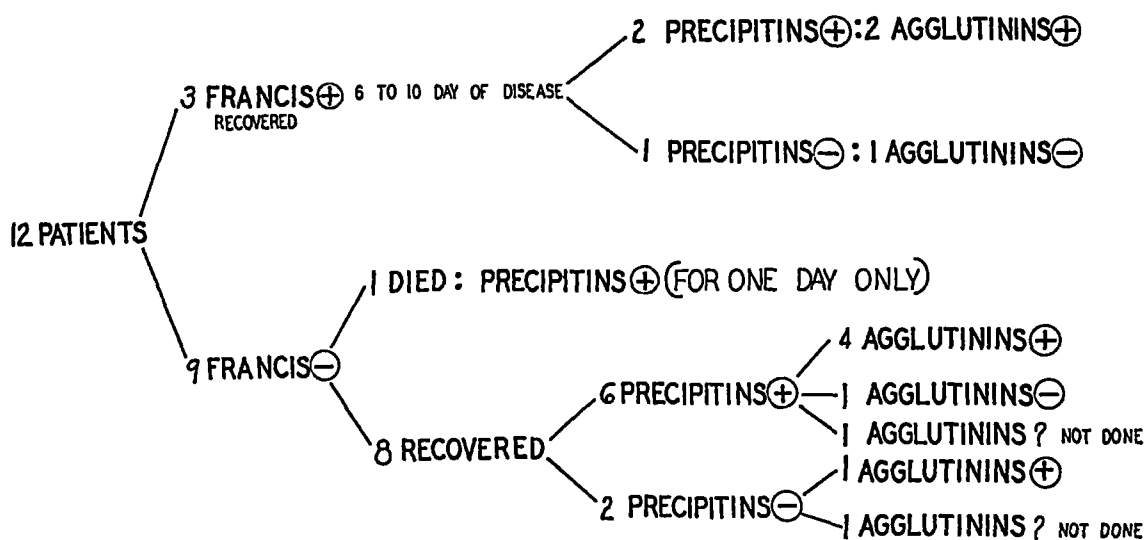


FIG 9 Immunity response to chemotherapy

of decapsulated and no longer type-specific pneumococci, another carbohydrate which is not type specific—the 'C' substance*. During the acute phase of illness, before specific immunity has developed, 'C' substance precipitates 'C' protein from the serum of patients suffering from pneumococcal, streptococcal, staphylococcal, *Bacillus Friedlander* infections, and also from infections due to some other agents. This substance is evidence of the presence of a bacterial irritant, because when it continues to be present the infection persists. It is not present in the mild bacterial infections or in those febrile conditions due to organisms which usually do not produce pneumonia. When 'C' substance fails to appear in pneumococcic pneumonia

* 'C' substance for these tests was generously supplied by Dr Walther Goebel of the Rockefeller Institute Hospital. The test was performed by adding 0.2 cc. 'C' substance, 1:10,000 to 0.2 cc of serum centrifuging 20 minutes at 2000 R P M and reading in a strong light with controls of saline and serums which have been negative. A faint but doubtful cloud with 10 gamma of 'C' substance in 0.4 cc of the serum and 'C' substance mixture was considered negative.

it may signify failure of response. It was not present in five very young children who died, two of whom showed demonstrable specific carbohydrate in the blood. In 417 adult pneumonia patients only 27 or 6.8 per cent failed to show it (figure 10). It was found in 89.5 per cent of cases treated or coming in before the fifth day. In those treated or coming in later, it was present in 96.1 per cent. Some of the patients did not have 'C' protein on the first examination but had it subsequently. In the patients coming in before the fifth day it appeared or was present on the second or third day. In 90 per cent of the patients showing it, it was present by the ninth day of disease. Twenty-eight were not examined for 'C' protein on discharge and

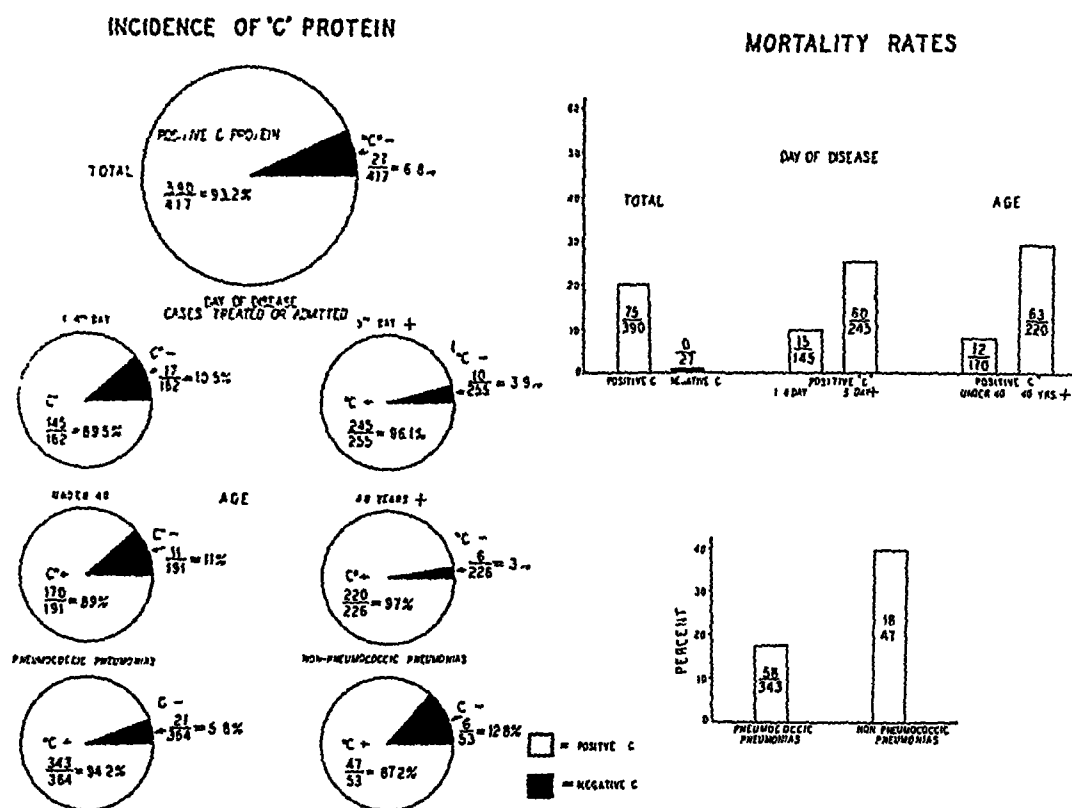


FIG 10 "C" protein adult pneumonias Nov 5, 1940-April 5, 1941

eight were discharged with 'C' still in the blood. It disappeared in over half the cases by the tenth day of disease. It was more frequently found in patients over 40 years (97 per cent) and in proved pneumococcal infections, 94.2 per cent. Among those patients who had 'C' protein the older patients, those treated late in the disease and those with non-pneumococcal pneumonias, showed the highest mortality (figure 10). There were no deaths among the 27 negative 'C' protein cases. In 15 per cent of cases the 'C' protein disappeared before the temperature fell. In the remaining 85 per cent of cases the 'C' protein disappeared within three days after the temperature fell. There were 23 patients who recovered when 'C' protein persisted

beyond three days, in 16 cases the pneumonia had not resolved, as shown by persisting signs, in one a bronchiectasis was suspected, serum sickness was present in five cases and pleural effusion in two cases. Of those who died when 'C' protein was present, i.e., 75 cases, 27 were patients who lived less than 24 hours after admission or after treatment was started. The other 48 deaths were in patients who had had more than one 'C' determination. In 13 of these the cause of death was a condition associated with the pneumococcal infection. Such conditions were pneumococcal meningitis in four cases, empyema in two instances, pericarditis in two cases (one having endocarditis as well), lung abscess in one, pleural effusion in one, and pulmonary edema in three. In nine of the patients who died therapy had failed because it was started late, in only one had it been commenced before the fifth day. In five more cases therapy failed because concentration of the drug was insufficient. There may have been unrecognized purulent conditions. In the other 21 cases death was due to an associated disease, 2 to pulmonary tuberculosis, 15 to cardiovascular renal disease (1 of whom died in collapse, 1 an excessively obese patient, 11 in cardiac failure, 1 with cerebral hemorrhage, 1 with azotemia). Other causes of death were diabetic coma (1), carcinoma of the esophagus (1), subphrenic abscess (1), rheumatic heart disease (1).

The study of 'C' protein response may be of value in diagnosis and in treatment when correctly interpreted. Its presence in large amount indicates response to an irritant and its disappearance after chemotherapy may indicate that a febrile episode is not due to continued infection or complication but possibly to the chemotherapeutic agent.

Causes of Failure with Chemotherapy When sulfonamide drugs given in the usual dose are ineffective in reducing the pulse and temperature of patients with pneumonia it is important to search for the explanation (table 1). The following should be thought of as possible explanations:

- (1) The diagnosis may be incorrect in that the consolidation may be due to organisms not affected by sulfonamides.

- (2) The concentration of the drug may be one that is ineffective. A low concentration may be due to insufficient dosage, poor absorption, excessive acetylation, or poor tissue penetration.

- (3) There may be too many organisms because the disease is treated late and the organisms are either not killed or are attenuated too slowly with the amount of drug present.

- (4) The pneumococci may have become fast. This is not frequent, but it does occur, and much higher concentrations of the drugs than usually employed may be required. Sometimes the organisms when grown in culture are killed by sulfapyridine, but in the presence of serum or exudates the drug is in part or completely inactivated by anti-sulfonamide substances. Unless very high concentrations are employed in such cases the drug fails as a therapeutic agent.

(5) When pneumococci are in pus collections, both the large number of organisms and the anti-sulfonamide substances may make chemotherapy ineffective whether the drug is administered either orally or parenterally. Sometimes in these purulent collections capsular carbohydrate and living organisms are present though absent from the circulating blood. As a rule, the immunity response and protection become exhausted unless surgical drainage is promptly employed. Evacuation, lavage and local application of sulfonamide drugs in very heavy concentrations have been proposed and used successfully.

(6) There may be severe toxic phenomena affecting the nervous system, the liver, the bone marrow and the kidneys or collapse may have been induced by the drugs.

(7) Finally, there may be, in certain patients, a failure of the immunity responses as already outlined so that the organisms that have not been killed may again become active. For the detection of such patients typing and studies of the immunity mechanism are necessary. Accurate data may make it possible to save the patient.

TABLE I

Causes of Failure of Chemotherapy

- 1 Wrong diagnosis
Pneumonia not due to sulfonamide affected organisms
- 2 Ineffective concentration due to non-absorption, conversion, rapid excretion or insufficient penetration
- 3 Too many organisms, late
- 4 Fastness—original or developed
- 5 Antisulfonamide substances, pus
- 6 Toxic action
- 7 Failure of immunity response

SUMMARY

The responses of the body to invasion of the pneumococcus have been presented, and it has been shown that there are immunity responses which contribute to recovery when sulfonamides are used. If treated very early in the disease, the pneumococci are attenuated or killed by these drugs. Immunity is established at the usual time as if the patient had had a mild infection and had recovered spontaneously. Although in most young patients other than infants, treated early, chemotherapy is sufficient completely to suppress the disease agent or to render it relatively innocuous, there are patients, those most severely stricken, who may require assistance, to them antibodies must be supplied to augment the immunity response. Moreover, when pneumococci resist chemotherapy because they are fast, they may respond to type specific serum therapy, and on this account specific typing and immunity study of blood and sputum are necessary for the best care of patients. When non-specific (for type) chemotherapy is employed patients who develop specific antibodies require neither serum therapy nor additional chemotherapy.

For such patients tapering off the drug is unnecessary and may be harmful. In addition to specific immunity, the diagnostic importance of the presence of acute phase or 'C' protein is discussed.

REFERENCES

- 1 OSGOOD, E E, BULLOWA, JESSE G M, BUKANTZ, S C, and BROWNLEE, INEZ The effect of sulfapyridine alone and with serum on pneumococcic pneumonia and pneumococcus infected marrow cultures, *Am Jr Med Sci*, 1940 cxcix, 364-380
- 2 FRISCH, ARTHUR W Sputum studies in pneumonia as an aid in prognosis, *Am Jr Clin Path*, 1940, x, 417
- 3 BULLOWA, J G M, DEGARA, PAUL F, and BUKANTZ, SAMUEL C Type specific antibodies in the blood of patients with pneumococcal pneumonia detection, incidence, prognostic significance and relation to therapies, *Arch Int Med*, January, 1942
- 4 BUKANTZ, S C, DEGARA, PAUL F, and BULLOWA, J G M Capsular polysaccharide in the blood of patients with pneumococcal pneumonia detection, incidence, prognostic significance and relation to therapies To be published in *Arch Int Med*

PROTEIN DERIVATIVES AS FACTORS IN ALLERGY¹

By ROBERT A. COOKE, M.D., F.A.C.P., *New York, N. Y.*

NUTRITIONAL or deficiency disturbances are seen in persons exhibiting manifestations that are allergic or are attributed to allergy. Occasionally, and especially in young children, genuine sensitizations to many common foods interfere with a sufficient and balanced diet and malnutrition results, but more frequently such disturbances arise from dietary restrictions imposed by the physician, based upon improper interpretation of or undue reliance on skin tests or to the acceptance without adequate proof of a patient's own story of food idiosyncrasies.

As my contribution to this Symposium on Metabolic Diseases, however, I am not going to dwell upon these aspects, but because of their present importance in the theory and practice of allergy I have chosen to consider the relation to allergy of certain metabolic derivatives of protein, namely, histamine, an end product capable of direct toxic effects, proteose, an early product of protein digestion which has antigenic capacity and acts only through the medium of antibody, and, very briefly, nucleic acid.

HISTAMINE

From the beginning of the studies in anaphylaxis by Richet, Theobald Smith, Otto and others, search was made for a hypothetical toxin, so-called anaphylatoxin, responsible for the characteristic symptoms of shock.

In the Herter Lectures delivered at the Johns Hopkins University in 1919, Dale² reviewed the discovery and the early studies on histamine by himself and his associates. On account of its physiological action, its potency and its presence in normal tissues, "the suggestion," as Dale says, "lay near at hand that the long-sought active substance was 'histamine,' and that the production of the latter in the system was the cause of the anaphylactic shock." These workers had demonstrated that histamine produced a contraction of smooth muscle fiber, it depressed capillary tone and rendered capillary walls permeable. In other words, when injected into animals it appeared to reproduce through the effects mentioned some of the more essential phenomena of anaphylactic shock. It was later shown that when injected intradermally it promptly created a typical allergic type of wheal. These findings revived an interest in anaphylactic studies but nothing much was accomplished until a method for the quantitative analysis of histamine was devised by Barsoun and Gaddum³ in 1935, later modified by Code³ in 1937. The method, however, is not a direct estimation of the

* Read at the Boston meeting of the American College of Physicians, April 23, 1941.
From the Department of Allergy, The Roosevelt Hospital, New York City.

organic base in fluids and tissues but a biological assay using smooth muscle contractility as the indicator. Such assays always give grounds for objection. In this particular instance substances other than histamine may be present which stimulate smooth muscle contraction, so that analyses are suggestive rather than conclusive.

On theoretical grounds the establishment of the fact that histamine is the active factor or even one of the active factors in anaphylactic shock would be important not only of itself but also because it might give a new basis for studies in certain allergic reactions of man. Space does not permit a critical review of recent experimental work in anaphylaxis. Suffice it to say that one is definitely impressed with the fact that many, perhaps most, workers believe that histamine is an essential, if not the factor in experimental shock. For example, Dragstedt,⁴ speaking of peptone reactions in dogs, says "We have been able to demonstrate that this reaction is accompanied by and due to the liberation of histamine just as is the case in anaphylactic shock."

While it seems likely that histamine is liberated in the shock, most workers have given little consideration to the possibility of other and perhaps even more important factors until the recent publication by Campbell and Nicoll.⁵ They showed that rat uteri, "unaffected by ordinary doses of histamine, respond in the tissue bath to some substance released by sensitized guinea-pig lung tissue during anaphylactic shock." Evidently some substance other than histamine was liberated.

In some recent (still unpublished) studies in my laboratory with Dis Wing and Stull we have come to a similar conclusion from a very elementary but different procedure similar to that of Schild.⁶ The sensitized guinea-pig uterine horn was suspended in the tissue-bath in Tyrode's solution and repeatedly shocked with histamine until it failed to contract, histamine remaining in the bath. When the horn had relaxed, antigen was added and a prompt and maximum contraction occurred. This is illustrated in figure 1. Thus, to quote Schild with whom we agree, "it would appear that either histamine released from the cell has a different action from that of histamine applied to the cell surface or it plays only a secondary part in anaphylactic shock." In experiments with atropinized muscle the results were the same, hence acetylcholine was not the factor.

In this connection, but without direct bearing on allergy, the important conclusions of Menkin⁷ in his studies on inflammation should be mentioned. Lewis⁸ has suggested that all capillary permeability in tissue injury was referable to a chemical H-substance, presumably histamine. Menkin's studies "indicate that the active factor recovered from an inflammatory exudate which is capable of inducing increased capillary filtration primarily by injury to the endothelial wall, does not seem to be histamine nor is it the H-substance in so far as its properties are supposed to resemble closely those of histamine." This substance finally isolated and crystallized by Menkin⁹

has been called leukotaxine. As a result of this work histamine is again deprived of its importance as the sole causative agent of increased capillary permeability.

I have discussed these various experimental studies because of their significance in the clinical studies with histamine that we shall now review. With regard to anaphylaxis, however, we must conclude that while histamine may be one factor, there are certainly others of equal or greater importance, the chemical nature of which is not yet known.

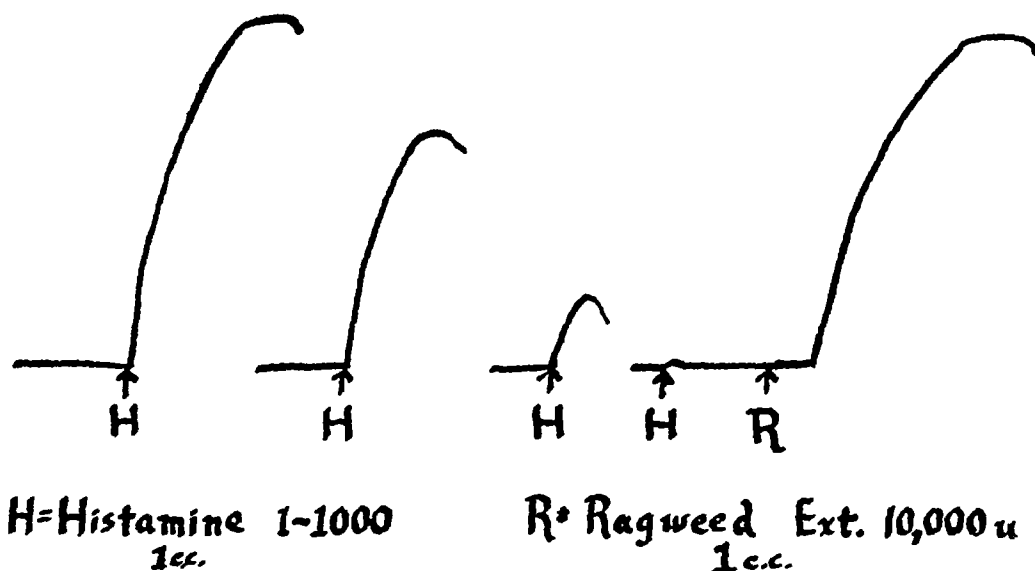


FIG 1 Histamine-antigen reactions of ragweed sensitive guinea pig uterus

Based upon the studies in anaphylaxis and because it produces an allergic type of wheal in the skin, histamine or H-substance, as Lewis⁸ prefers to call it, is blamed by one or another investigator, definitely or by implication, for such clinical conditions as traumatic shock, serum shock, serum disease, angioedema, vasomotor rhinitis, asthma, eczema, various types of headache, Menière's disease, and the urticarias, including those due to physical agents.

Let us examine certain clinical aspects more fully. The statement is made that if a spontaneous urticarial wheal appears in a certain area it will not reappear in that area for 36 to 48 hours, the skin is unresponsive, due presumably to a failure of the cells to form the H-substance. Alexander^{10, 11} has observed this in urticaria due to cold. I, myself, with a much more limited experience, have not been able to verify this, either for the spontaneous wheal or for that due to cold. In fact, in one of my patients with cold allergy the reapplication of ice to the wheal site made 24 hours previously led to a more rapid and greater wheal than the first application. In this same patient the right hand was immersed in ice water until edema was produced. Three hours later both hands were immersed in ice water. The edema that developed in the right hand was greater and more prompt than that of the left. Unresponsiveness was not demonstrated. Such exceptions to the rule are not adequately explained by the present theory, nevertheless

the so-called unresponsive phase has been made the basis for and, as Alexander says, "may well explain the successful treatment of chronic urticaria with daily injections of histamine since histamine presumably provokes the production of H-substance" He further says that histamine injections were given "on the theory that H-substance would be released generally The unresponsive phase was maintained by daily subcutaneous treatment," and "it was surprising to discover the degree of tolerance that could be established" This latter point of view is upheld by Farmer¹² and others

The majority of writers on clinical effects of histamine fail to discuss its theory, content to rest their case on the clinical results of histamine therapy The theory, however, is inconsequential—it is the fact, the result, that counts, and so far as I can observe, the results of histamine therapy are reported as quite uniformly successful No definitely adverse reports have recently appeared

With some reluctance, therefore, I feel impelled to record the experiences that I and my associates have had with histamine They may be summarized as follows (1) Normal non-allergic persons and allergic patients when skin tested with histamine solutions react alike A slight positive intracutaneous reaction first develops with a dilution of 1–10,000,000 of histamine base, that is 10^7 with a range from 10^6 to 10^8 This means that there is no greater reactivity to histamine in the allergic than in the non-allergic group This agrees with similar findings of Gotsch¹³ and of Lass,¹⁴ and contradicts the theory that allergic persons are more reactive to histamine than normal non-allergic persons

(2) Using subcutaneous injections, beginning with 0.01 milligram of histamine base, we could increase the dose up to about 0.1 milligram, at which level a good general reaction with flushed face resulted in 90 per cent of the 20 allergics and of the 40 non-allergic normal controls There was no difference between the two groups But more significant still, no increase of tolerance was observed nor could it be obtained in either group by long continued injections once a definite but slight pharmacological effect was produced Larger doses could be given but always with greater reaction

(3) Therapeutic injections were given to 10 patients with urticaria over periods of 4 to 12 weeks and in no case did we observe any improvement Daily injections were used the first week, beginning with very small doses and increasing up to the first sign of slight reaction, usually 0.1 milligram or slightly more of histamine base, which dose was then given every other day for at least a week, then twice a week, and finally once a week Desensitization is the term applied to this treatment by some This seems to me erroneous if used in its immunological sense, and since we are dealing with an immunological problem it should be used in this sense

(4) Two years ago in my clinic, Hampton studied the blood of five patients taken during and after constitutional reactions induced during the course of pollen therapy and of two patients with severe giant urticaria

Code's technic was used. In no case was there evidence of an increase of blood histamine during the allergic reaction.

In short then, with regard to clinical studies, my results are not in accord with most of those reported. I find no unresponsive phase in urticaria, no increase of tolerance to histamine, no clinical result in chronic urticaria, and no evidence that histamine is increased in the blood during general allergic reactions. I believe, therefore, a critical and even a skeptical point of view is still warranted, both as to the rôle of histamine in allergy and as to the therapeutic benefits to be derived through its use. Not that one objects to its general use, in fact we should favor it, for thus its true value or lack of value will the sooner be established, just as happened recently with that other widely heralded allergy remedy—histaminase.

PROTEOSES

The second protein derivative to be considered is proteose. The development of sensitization in animals to substances other than natural proteins has generally been regarded as impossible. Lipins, polysaccharides and simple chemicals are spoken of as antigens, but they stimulate antibody formation only when bound to protein and therefore are not antigens—generators of antibody—in the strict sense of the word, but are rather determinants of specificity, called "haptens" by Landsteiner,¹⁶ with a capacity only for reacting with preformed antibody.

The digestion products of protein, such as proteose, have likewise been considered as non-antigenic and I find no evidence that they may behave as haptens. Fink¹⁶ fully reviewed the work up to 1914 and concluded that any claims for antigenicity of proteoses were based on unsatisfactory evidence. Since then relatively little work has been done, but such as has been done by Zunz¹⁷ and others is definitely unconvincing and the consensus, as expressed in the textbooks on immunology by Gay¹⁸ and Zinsser¹⁹ is that capacity for producing or reacting with antibody has been lost in the earliest stage of protein breakdown.

By a series of rather strange coincidences, I and some of my associates were led to reinvestigate the question of sensitization to primary and secondary proteoses. In brief, the story begins with the observation of a fairly severe allergic reaction, occurring promptly after the second injection of tetanus toxoid, in a patient in the Fall of 1938. Such reactions have been noted by Jones and Moss,²⁰ Hall,²¹ Gold,²² Parish and Oakley,²³ Whittingham,²⁴ and Cunningham.²⁵ Our studies²⁶ of this case showed that a sensitization had developed to the supposedly non-antigenic protein derivative, proteose, used in most tetanus culture media and present in the toxoid. This stimulated our interest in the anaphylactogenic possibilities in animals and experiments with the commercial peptones on guinea-pigs yielded positive Dale reactions in 18 of 19 trials.

Extended studies by some of my associates²⁷ with proteoses prepared

from known sources showed definite and new specificity in the experimental guinea-pig for a number of them, such as the primary proteose of milk whey and casein and the proteoses of beef and chicken. The question then arose as to the significance of such findings in certain of the food sensitivities of men. Since products in the early stages of digestion are antigenic, a means might be at hand to explain and to diagnose certain definite clinical reactions after the ingestion of foods that give negative skin tests when the original protein is tested. A correct and definite diagnosis of food sensitivity would be of value because today, among those interested in the field of allergy, there is a wide diversity of opinion as to the incidence of food sensitization. This difficulty is due in part to the fact that skin tests are often positive to a food that can be eaten with impunity and conversely, tests may be negative to foods that definitely cause clinical reactions. The former may be explained on the basis that skin reacting foods are altered by digestion and absorption and never reach the sensitized cells in sufficient amounts to set up a clinical reaction. The second observation, negative tests with clinically reacting foods, deserves further comment. The usual positive skin test with pollen extract in hay fever subjects is an immediate reaction. The clinical reaction following absorption of pollen from the air is likewise an immediate reaction. That the clinical reaction must follow immediately upon contact of an antigen with the sensitized cell seems to me a self-evident fact inherent in the immunological nature of such antigen-antibody-cell combinations. In the reactions to inhaled allergens, such as pollens, this is exactly what takes place. With the skin reacting and clinically reacting food allergens there may be an apparent delay of the symptoms up to perhaps one hour, due to the slower absorption through the gastrointestinal tract.

What then may be said regarding the allergies to ingested food that regularly develop several hours after the ingestion of a particular food which gave no skin reaction on test? At a meeting of the American College of Physicians in Boston in 1929, I presented a paper on "The Delayed Type of Allergic Reactions"²⁸. The clinical features of the four cases presented were (1) that a food was the factor in all the cases, (2) following the ingestion, reaction was delayed up to 30 hours, (3) the reaction or incubation time was quite definitely fixed in each case, (4) the skin reaction to the original food was always negative before as well as after the clinical reaction. It was later suggested²⁹ that the real antigen in such cases might be a derivative of the food, something elaborated by the body from the food, and if this product were known and tested it might give a positive reaction. Now our story begins to link up with the observations on proteoses. Using solutions of primary and secondary proteoses prepared from known sources, we have tested a series of 39 allergic persons and found five that gave a positive skin test and positive passive transfer test but were negative to test with the original protein.

Let me present briefly the important features of one of the five cases studied. C. Z., male, 30, first seen in September 1938. He was admitted to the Roosevelt Hospital with severe status asthmaticus which began 25 days prior, following a respiratory infection. He was sensitive to ragweed



FIG 2 Six hours after barium without milk

Food tests were negative and there was no definite history of food idiosyncrasy or aversion, but the patient was suspicious that milk did not agree with him. He had also a chronic sinusitis involving the left antrum. In spite of attention to the indicated causes of his asthma, he was not doing well and

was unable to work most of the time In January 1940 he was tested with the proteose preparations and gave a good positive reaction to the primary proteose of milk whey and a slight reaction to the secondary proteose Passive transfer with his serum was likewise positive on a normal test-subject



FIG 3 Six hours after barium and milk

Later on he was admitted to the hospital for observation On a certain day when free of asthma he was given a quart of milk to drink—in two hours he developed nausea, then mild asthma, later he had abdominal pain and several loose stools His asthma increased and lasted 12 hours This clinical trial

was made on two other occasions with the same results. As evidence of asthma, in addition to physical signs, is the fact that on one day before having milk the vital capacity was 2580 c c, whereas 5½ hours after having milk it was only 1220 c c. Gastrointestinal roentgen-rays were made without and with milk in the barium meal. The contrast was definite. Dr Boone's report says that "Without milk the six hour film (figure 2) shows the stomach empty, with the head of the barium meal in the transverse colon." The six hour film after milk-barium (figure 3) shows "increased motility of the meal in the small bowel. There is considerable residue in the stomach. The entire colon was outlined as early as four hours." Abnormal segmentation of the small intestine was a definite feature.

Thus it seems to me it has been shown that clinical sensitization to protein digestion derivatives, at least at the proteose stage, exists. This helps to explain the "delayed" type of food reactions as previously postulated and suggests a method of approach in the diagnosis of a certain limited number of food allergies.

NUCLEIC ACID

Another protein derivative that may be briefly mentioned is nucleic acid, which is commanding the attention of immunologists on account of its bearing on serological reactivity. This would not call for special mention here were it not for the recent findings of Winkenwerder, Buell and Howard³⁰ that 50 ragweed pollen sensitive patients gave typical immediate wheal-erythema reactions when tested with dilute solutions of nucleic acids and many of their derivatives. The skin sensitizing antibody was found in the serum of 10 of their patients by the method of passive transfer, and two patients had typical severe constitutional reactions from the skin test. Sherman, in my clinic, has tried out this test and observed reactions in certain ragweed sensitive patients. The significance of this sensitivity is not at all clear as yet. It is tempting but unwise to stress the importance of such findings or theorize on their possible clinical application.

In closing let me say that I have tried to present some picture of present day trends in the study of allergy. Protein derivatives which a few years ago were considered devoid of antigenic or hapten significance are now found to be of some importance. Studies are proceeding in an attempt to determine the chemical basis of allergic reactions as well as the serological evidence for and the chemistry of the induced immunity.

REFERENCES

- 1 DALE, SIR HENRY H. Capillary poisons and shock, anaphylaxis, chemical structure and physiological action, *Bull Johns Hopkins Hosp*, 1920, xxxi, 257, 310, and 373.
- 2 BARSOUM, G. S., and GADDUM, J. H. The pharmacological estimation of adenosine and histamine in the blood, *Jr Physiol*, 1935, lxxxv, 1.
- 3 CODE, C. F. The quantitative estimation of histamine in the blood, *Jr Physiol*, 1937, lxxxix, 257.

- 4 DRAGSTEDT, CARL A Anaphylaxis and allergy, *ANN INT MED*, 1939, xiii, 248
- 5 CAMPBELL, DAN H, and NICOLL, PAUL A Studies on in vitro anaphylaxis and release of an active non-histamine material from sensitized guinea-pig lung, *Jr Immunol*, 1940, xxxix, 103
- 6 SCHILD, H The reaction of the guinea pig uterus to histamine and anaphylaxis, *Jr Physiol*, 1936, lxxxvi, 51
- 7 MENKIN, VALY Studies on inflammation XII Mechanism of increased capillary permeability A critique of the histamine hypothesis, *Jr Exper Med*, 1936, lxiv, 485
- 8 LEWIS, SIR T The blood vessels of the human skin and their responses, 1927, Shaw and Sons Ltd, London
- 9 MENKIN, VALY Studies on inflammation XIV Isolation of the factor concerned with increased capillary permeability in injury, *Jr Exper Med*, 1938, lxvii, 129
- 10 ALEXANDER, H L Treatment of allergic disorders with histamine and histaminase, *Jr Lab and Clin Med*, 1940, xxvi, 110
- 11 ALEXANDER, H L Allergic syndromes in the absence of allergens, *Jr Allergy*, 1940, xi, 163
- 12 FARNER, LAWRENCE Histamine in anaphylaxis and allergy, *Bull New York Acad Med*, 1940, xvi, 618
- 13 GOTSCH, K Hyperergische Phaenomene und Histamine, *Ztschr f klin Med*, 1936, cxxix, 593
- 14 LASS, E Jod- und Histaminempfindlichkeit der Haut bei Tuberkulosen, *Ztschr f Tuberk*, 1933, lxxvii, 350
- 15 LANDSTEINER, KARL The specificity of serological reactions, 1936, Charles C Thomas, Baltimore
- 16 FINK, E B The antigenic properties of proteoses, *Jr Infect Dis*, 1919, xxv, 97
- 17 ZUNZ, M Nouvelles recherches sur l'anaphylaxie par les protéoses et les autres produits de desintégration de proteines, *Bull Acad roy de med de Belgique*, 1923, iii, 426
- 18 GAY, F P, and others Agents of disease and host resistance, 1935, Charles C Thomas, Baltimore, p 335
- 19 ZINSSER, HANS, ENDBERS, J F, and FORBES, L D Immunity principles and application in medicine and public health, 1939, The Macmillan Co, New York, p 33
- 20 JONES, F G, and MOSS, J M Studies on tetanus toxoid 1 Antitoxic titer of human subjects following immunization with tetanus toxoid and tetanus alum precipitated toxoid, *Jr Immunol*, 1936, xxx, 115
- 21 HALL, W W Active immunization against tetanus with tetanus toxoid, *Mil Surg*, 1937, lxxx, 105
- 22 GOLD, H Active immunization of allergic individuals against tetanus by means of tetanus toxoid, alum precipitated refined, *Jr Allergy*, 1938, ix, 545
- 23 PARISH, H J and OAKLEY, C L Anaphylaxis after injection of tetanus toxoid, report of a case, *Brit Med Jr*, 1940, i, 294
- 24 WHITTINGHAM, H E Anaphylaxis following administration of tetanus toxoid, *Brit Med Jr*, 1940, i, 292
- 25 CUNNINGHAM, A A Anaphylaxis after an injection of tetanus toxoid, *Brit Med Jr*, 1940, ii, 522
- 26 COOKE, R A, HAMPTON, S F, SHERMAN, W B, and STULL, A Allergy induced by immunization with tetanus toxoid, *Jr Am Med Assoc*, 1940, cxiv, 1854
- 27 STULL, A, and HAMPTON, S F Antigenic studies of proteoses, *Jr Immunol*, 1941, xli, 143
- 28 COOKE, R A The delayed type of allergic reaction, *ANN INT MED*, 1930, iii, 658
- 29 COOKE, R A Gastrointestinal manifestations of allergy, *Bull New York Acad Med*, 1933, ix, 15
- 30 WINKELWIEDER, W L, BUELL, M V, and HOWARD, J E The sensitizing properties of the nucleic acids and their derivatives, *Science*, 1939, xc, 2337

THE TREATMENT OF ACUTE CARBON TETRACHLORIDE POISONING WITH A REPORT OF TWO CASES *

By BENJAMIN R. ALLISON, M.D., F.A.C.P., *Hewlett, Long Island*

THE purpose of this paper is four-fold (1) to present two cases of acute carbon tetrachloride poisoning (one fatal, with autopsy), (2) to discuss the treatment of this condition, (3) to call attention to the health hazard involved in its widespread use, and (4) to suggest that it be included in textbooks as a disease entity

CASE REPORTS

Case 1 A nine-year-old boy, who had smeared red chalk on the covers of his bed, took a tin of cleaning fluid from the cupboard and in the process of cleaning found that he liked the odor of the fluid and the way it made him feel. He poured a considerable amount on the blanket, replaced the tin and crawled into bed. He said that he saw stars and then couldn't remember anything. When his father entered the room a few minutes later he found the boy under the covers, completely unconscious and breathing noisily. The physician on arrival, found the child unconscious, his face flushed, perspiring moderately, pupils dilated, pulse rapid and thready, and all deep and superficial reflexes absent. No clue could be found as to what had happened to him. No medicine bottles were found in the room, and there was no evidence that the medicine chest had been disturbed. His stomach was washed out, three grains of caffeine sodium benzoate were given hypodermically, and he was kept warm. In about one hour he became restless. He was catheterized, and the urine showed two plus sugar. Fifteen units of insulin were given. In another hour he had begun to regain consciousness, but as the diagnosis was not clear he was moved to the Nassau Hospital where 15 more units of insulin were given. Soon after, he was able to tell the story of what had happened, and it was evident that he had been anesthetized by carbon tetrachloride as was proved later by inspection of the container. Physical examination at this time revealed nothing further except an area of hyperemia on the outer mid-thigh to mid-calf region of one leg.

COURSE OF DISEASE

He was in the hospital six days. Immediately on admission blood examination showed a CO_2 content of 48 volumes per cent and 213 mg per cent of sugar. The urine showed 14 per cent sugar and a trace of acetone. He was given 1000 c.c. of normal saline intravenously. He vomited persistently and after a few hours was given a colonic irrigation and 750 c.c. of 5 per cent glucose in saline intravenously. In 12 hours the vomiting stopped and he vomited only twice subsequently. During the first day he was drowsy much of the time and was irritable when awake. That evening his temperature rose to 104.5°F , pulse 120, respirations 28. The temperature stayed around 104° for 16 hours, then fell to 100.5° . The subsequent evening temperatures were 100°F . The blood calcium determination, 16 hours after the onset, was 12.9 mg, so calcium was not given intravenously, but 60 grains a day were given by mouth. As he took fluids well after the first day, no more were given intra-

* Received for publication February 6, 1941

From the medical service of the Nassau Hospital, Mineola, Long Island

venously Thirty grains of sodium chloride were given four times a day for two days

On the first day there was tenderness and some rigidity over the upper abdomen and considerable distention On the second day the liver edge could be felt about 4 cm below the costal margin, the sclerae were slightly yellow, and a trace of bile appeared in the urine The tenderness and rigidity in this area persisted, gradually improving until, on discharge, enlargement and tenderness of the liver were the only positive physical signs Pain and distress in the upper abdomen which were marked during the first two or three days slowly improved The superficial burn on the leg and thigh was dressed On the second day the diet consisted of fluids, water, fruit juices to which lactose was added, and gingerale On the third day he was started on a diet of carbohydrate 350 gm, protein 75 gm, and fat 50 gm, which was continued

On returning home, the child was kept in bed for three weeks because of the persistence of liver enlargement and a slight evening elevation of temperature A high carbohydrate diet was continued and he received no other treatment The liver could not be palpated after one month, so, in spite of the fever, the child was allowed up It was found that after slight exercise the temperature rose to 100° F, 100 5° F, and, on one or two occasions, a little higher, so his exercise was increased very gradually No cause, other than exertion, could be found to account for the fever His activity was slowly increased until, after three months, he was leading a normal life

LABORATORY FINDINGS

Urine While in the hospital nine specimens were examined Only the first showed sugar On five occasions one plus albumin was present and on three occasions a few casts were found Red blood cells were found only once Bile was present from the second day to the sixth day After returning home six specimens were examined, the last on September 15, and always found to be normal

	Hemoglobin	Red blood cells	White blood cells	Polymorphonuclear leukocytes	Eosino- philes
First day	95%	5 8	22,400	93%	4
Third day	100%	5 3	12,100	52%	
Twelfth day	80%	4 6	6,400	78%	
Twenty-first day	76%	4 8	6,200	68%	

Blood Sugar On admission the blood sugar was 213 mg, eight hours later 90 9 mg, second day 119 mg, fourth day 111 mg, twelfth day 80 mg Blood CO₂ determinations were 48, 46, 38, 48 respectively Icteric index was 8 and 7 2 Blood calcium was 12 9 mg on the first day Blood sedimentation rate on the twelfth day was 18 mm per hour, and on the twenty-first day, 14 mm per hour A roentgen-ray of the lungs was normal on the seventeenth day

DISCUSSION

This boy received a large dose of carbon tetrachloride by inhalation He was completely anesthetized for over two hours. It is possible that there was also absorption through the skin, as there later appeared a large area of hyperemia and burn on the thigh and leg which had been in contact with the wet bed covers In the absence of history, when sugar was found in the urine, diabetic coma was considered a possibility It was not until the

second day that definite evidence of liver damage occurred, i.e., an enlarged, tender, painful liver, a trace of bile in the urine, high fever and leukocytosis. The importance of early intravenous administration of calcium and glucose was not appreciated, and since the blood calcium was high calcium was given only by mouth. Fluids and medication given by mouth were nearly all retained after the first day. There was very little evidence of kidney damage. No central nervous symptoms occurred. The management of the case after the acute phase was determined by the results of tests which showed the degree of liver repair. Liver tenderness persisted for two weeks and enlargement for a month. These physical signs, plus evening fever, increase in polymorphonuclear leukocytes in the blood, and a slightly elevated blood sedimentation rate indicated that repair was not complete in three weeks. During the next six weeks an elevation of temperature to between 100° F and 101° F on slight exercise indicated continued disturbance, as no other cause could be found for this fever.

Case 2 A 48-year-old carpenter was admitted to the hospital after having drunk a cleaning fluid containing carbon tetrachloride. His past history was negative except that he was a steady consumer of alcohol. In fact, when the accident occurred he had been drinking and in the dark poured another drink from the wrong bottle. Almost at once he began to vomit persistently, followed by diarrhea which later produced "very dark colored" stools. He felt as though he had a fever and was very drowsy. At times he was delirious. The day before admission he noticed that his abdomen was markedly enlarged. He had not urinated for three days. He had been treated at home symptomatically, and had been given glucose twice intravenously after he became anuric.

He was admitted to the hospital on the eighth day of his illness. Physical examination showed an obese, intensely jaundiced, critically ill man. He was quite stuporous and responded to questioning with difficulty. His legs and ankles showed a two plus edema. His pharynx was injected and slightly edematous. There was a systolic murmur localized at the apex. Blood pressure was 160 mm Hg systolic and 80 mm diastolic. His abdomen was greatly distended, with signs of fluid, and there was tenderness over the liver region.

He was in the hospital 44 hours, dying on the tenth day of his illness. He grew steadily worse, becoming cyanotic and comatose on the second day. His temperature was never over 100° F. The pulse varied between 72 and 118. His respirations were labored and the rate around 30 per minute. He had no twitching or convulsions. He vomited once, a large amount of coffee-ground material. He was catheterized at once on admission, and 30 c.c. of dark colored urine were obtained which showed three plus albumin, sugar 0.4 per cent, bile three plus, and microscopically many fine and coarsely granular and hyaline casts, 10 to 15 red blood cells and eight to 10 white blood cells, per high power field. Blood non-protein nitrogen was 160 mg, sugar 222 mg, creatinine 6 mg, icteric index 100, CO₂ 35 vol per cent. Blood count hemoglobin 85 per cent, red blood cells 3.3 million, white blood cells 10,300 with 81 per cent polymorphonuclear leukocytes.

TREATMENT

Soon after admission he was given a colonic irrigation which returned a "dark black liquid". He received five intravenous injections of 50 c.c. of 50 per cent glucose, each of which was followed by 25 units of regular insulin. He was given

daily 1200 cc of fluids by mouth including water, fruit juices and milk. He vomited only once so most of this was retained. He was catheterized on the second day, and only 3 cc were obtained. An abdominal paracentesis was attempted on the second day, but, for some reason, no fluid was obtained. He did not void any urine while in the hospital. Oxygen was administered on the second day.

An autopsy was performed with the following positive findings. The skin and sclerae were deeply jaundiced. There was a large amount of bile-stained fluid in

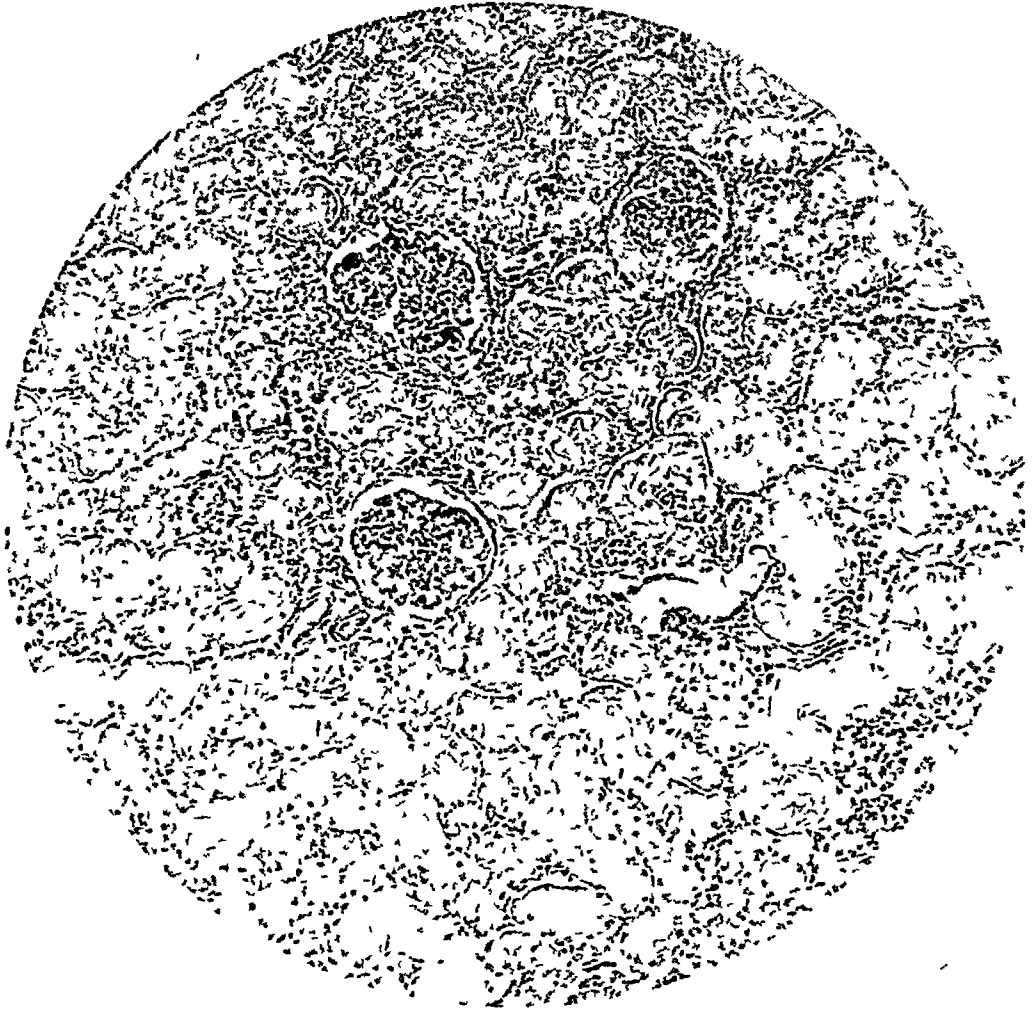


FIG 1 Kidney ($\times 50$)—showing cloudy swelling and necrosis of the tubular epithelium. The glomerulus in the upper right segment shows albuminous exudate in the intracapsular space.

the abdominal cavity. The epicardium was somewhat congested and showed scattered petechial hemorrhages. The liver weighed 2350 gm, and was pale brown in color. On section the cut surfaces presented numerous hemorrhagic areas in which the normal pattern was indistinct. The spleen weighed 390 gm, and the pulp was mushy. The adrenals appeared normal. The kidneys weighed 300 and 290 gm; the capsules stripped with difficulty, the cut surfaces were grossly congested and contained numerous hemorrhagic areas as did both pelves. There were extensive petechial hemorrhages in the bladder mucosa. The pancreas also showed a few scattered

hemorrhages The stomach, the small and large intestines showed numerous scattered hemorrhagic areas A trace of carbon tetrachloride was found in the brain but not in the liver or kidneys

MICROSCOPIC EXAMINATION

Liver "Sections show extensive pathological change There are large areas of necrosis with associated hemorrhage, these are located for the most part away

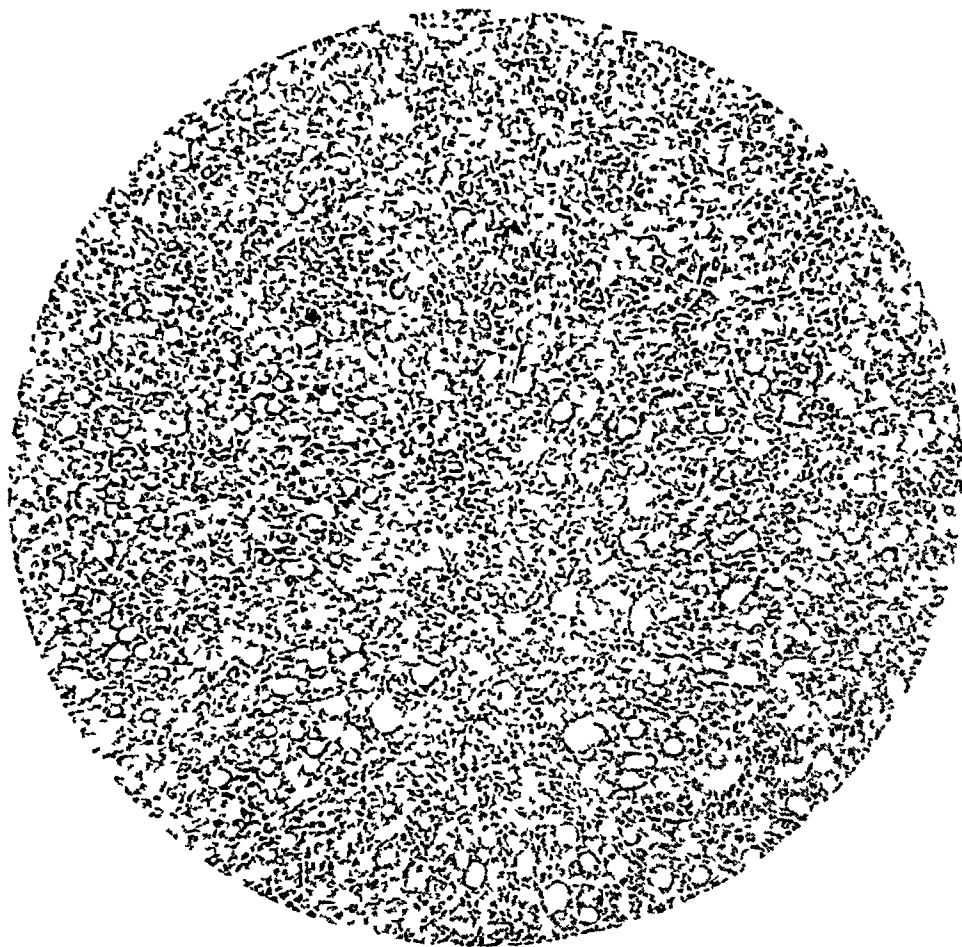


FIG 2 Liver ($\times 50$)—showing focal necrosis and extensive fatty metamorphosis of the liver cells

from the portal systems and more toward the center of the lobules In addition, there is widespread fatty vacuolization of the liver cells There is a moderate increase of the round cells in the periportal spaces "

Kidney "Sections show marked degenerative changes in the tubules varying from cloudy swelling to actual necrosis The glomerular tufts are engorged The capsular spaces contain albuminous exudate Some of the glomerular tufts are adherent to the capsule In an occasional glomerulus, free red cells are seen in the capsular spaces The blood vessels are normal "

Spleen "Sections show moderate to marked engorgement of the pulp with red cells. Many irregular particles of extracellular brown pigment are present. The follicles are normal."

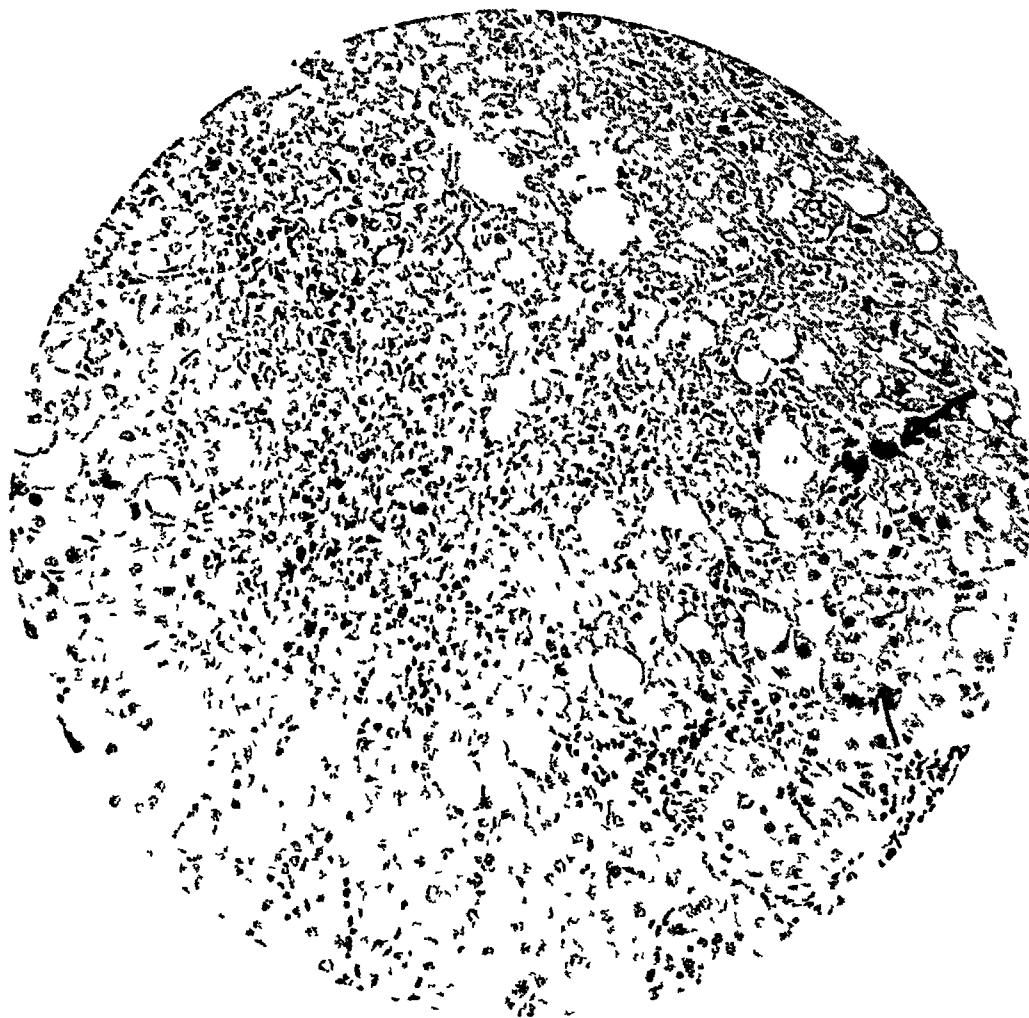


FIG. 3 Liver ($\times 250$)—showing higher magnification of necrotic zones. The large hyperchromatic nuclei (arrow) suggest regenerative changes.*

DISCUSSION

This man was reported to have drunk a "furniture polish" used for cleaning purposes. Due to unusual circumstances surrounding the case the exact nature of this fluid was not known and it was labeled with an unfamiliar trade name. The medical examiner recovered the original container and found it to have a high carbon tetrachloride content. The man was an alcoholic and had been imbibing before he drank the fatal portion thinking it to be whiskey. Its toxicity was undoubtedly increased by alcohol. It was also taken after he had eaten, which again made it more toxic. When

*I am indebted to Dr. Theodore J. Curphey, Medical Examiner of Nassau County, for his interpretation of the pathological findings, and to Mr. David Skelton, staff photographer, for the photomicrographs.

he reached the hospital on the eighth day, he presented an extreme picture of acute gastroenteritis, hepatitis and nephritis. The autopsy confirmed the clinical findings showing degenerative changes in the liver with a marked central necrosis, involvement of both the glomeruli and tubules of the kidneys, and extensive hemorrhage into the mucosa of the gastrointestinal tract and in other organs. These are the typical end result of this type of poisoning.

TREATMENT OF ACUTE CARBON TETRACHLORIDE POISONING

Two drugs, calcium and glucose, are definitely indicated in the treatment of carbon tetrachloride poisoning. The importance of this treatment does not seem to be generally recognized as was shown in the management of the two cases herein reported.

What is the rôle of calcium in the treatment of this condition? The following investigators have contributed to our knowledge of this subject. Lamson, Minot and Robbins¹ from experiments on dogs found that carbon tetrachloride was much more toxic and caused greater liver damage in animals fed on a low calcium diet than in those fed on a normal or high calcium diet. They also showed that symptoms of intoxication were promptly relieved by the intravenous administration of calcium. They thought that the central necrosis of liver cells increased the bilirubin in the blood and that bilirubin entered into a complex combination with calcium. Thus, though the total blood calcium be normal or high, the active or ionized calcium may be low. Symptoms of lack of available calcium sometimes ensued, such as tremors, convulsions, tetany and tendency to hemorrhage.

Wokes² fed mice on low and high calcium diets plus cod liver oil and found little difference in the response of the two series after giving a toxic dose of carbon tetrachloride. He did find, however, that calcium given one hour before administration reduced the mortality but did not completely protect the liver.

Cutler,³ in studies on large series of dogs, found that in 131 animals fed on a diet of lean meat without bones, 98 died after a toxic dose of carbon tetrachloride; whereas, in 98 dogs fed on lean meat and calcium salts, only 18 died. All showed in a few hours an increase in guanidine in the blood and subsequent hypoglycemia. To protect against intoxication they suggest that a diet should not tend to increase guanidine as does meat, should be rich in calcium to combat hyperguanidinemias, and high in carbohydrate to relieve hypoglycemia. Minot⁴ demonstrated a similar increase in guanidine in the blood followed by hypoglycemia after liver injury, and showed that symptoms of guanidine intoxication are similar to those of carbon tetrachloride poisoning. He discussed the effect of this guanidine accumulation on the carbohydrate metabolism and found that the administration of calcium salts hastened recovery. The giving of glucose alone did not prevent death in experimental animals, but calcium did. He concluded that the exact mechanism of this beneficial action of calcium is not known.

It seems, therefore, that calcium plays an important rôle in protecting against liver damage and curing symptoms of intoxication from carbon tetrachloride. It would appear rational to administer calcium and glucose as soon as the diagnosis is made and continue it until all evidences of liver damage have disappeared. Even in the absence of signs of liver damage calcium should be given for four or five days. A normal blood calcium does not mean that calcium is not needed, for in this condition part of the diffusible or usable calcium may combine in some non-usable form and still be present in the blood. Calcium therapy has been successfully applied in several cases reported in the literature.

How should calcium be administered? In dealing with a normal digestive apparatus it would seem that giving calcium by mouth every four to six hours would maintain an adequate blood level. In acute carbon tetrachloride poisoning with involvement of the gastrointestinal tract and liver the absorption is not normal, and even though food is retained we do not know how it is utilized. Therefore, essential fluids, hypertonic glucose and calcium should be given intravenously, at least until we know that they can be absorbed from the intestinal tract. In severe cases this should be done every five or six hours, the interval lengthened as the patient is able to take and assimilate fluids and food. If nephritis is present and edema appears, making it necessary to limit fluids, a small amount of a higher concentration of glucose (50 cc of a 50 per cent solution) should be given. If jaundice and signs of liver involvement occur, the intravenous route should be used if necessary for from one to two weeks. Blood chemical studies will materially help in ascertaining the degree of liver and kidney damage and so determine when treatment can be safely terminated.

It is also important to know how soon liver damage occurs and when liver cell repair is complete. The liver has great regenerative ability and functions efficiently if a small part of it remains normal, as was shown by Bollman and Mann⁵. Lacquet,⁶ and Cameron and Karunaratne⁷ have studied the rate of liver destruction and repair in rats. After administering a toxic dose of carbon tetrachloride, destructive changes begin in a few hours, becoming extensive in 24 hours and continuing so for three or four days. In three to five days signs of regeneration can be seen and after two weeks repair is complete.

Peery⁸ had occasion to observe autopsies of three patients who simultaneously drank carbon tetrachloride. One died in six hours and showed no change in the liver; the second died in 68 hours and showed extensive necrosis and hemorrhage, and the third died after 150 hours showing extensive damage but evidences of regeneration taking place. In our inhalation case the liver was swollen and tender on the second day when a trace of bile appeared in the urine. Two or three days may elapse before liver damage manifests itself so it is better to assume that liver damage exists and treat it at once.

Earlier writers made little mention of kidney damage, although it oc-

curied in some of the cases reported Franco,⁹ in 1936, called attention to the frequency of kidney involvement and reviewed the literature with respect to this point Other cases have since been reported and Semetra¹⁰ in 1939, from a collected series of 141 cases found that 33 gave clinical evidence of renal involvement, and 17 of the 25 autopsies showed anatomical evidences of renal disease Both of our cases showed signs of kidney involvement Case 2 showed extensive damage at autopsy As far as treatment of the kidney is concerned, no conflict in the choice of therapy arises because of the involvement of both liver and kidney Stomach lavage, colonic irrigation, forcing of fluids and glucose and calcium intravenously all tend to protect the kidney and constitute sound treatment should serious kidney damage be present

If hemorrhage into the gastrointestinal tract occurs, especially if associated with liver damage and lowered fibrinogen, calcium is useful If there is considerable blood lost, transfusion with blood or blood plasma is indicated

Eye symptoms, such as blurred vision and toxic amblyopia, have been described from carbon tetrachloride intoxication but disappear as the intoxication is combated

Forbes and Neale¹¹ demonstrated a substance isolated from liver extract which protected rat livers against necrosis following carbon tetrachloride inhalation With their associates^{12, 13, 14} they later showed this substance to be sodium xanthine and found that other purines gave like protection This action of xanthine was confirmed by Barrett, MacLean and McHenry,¹⁵ and Fitzhugh¹⁶ Whether this principle is applicable to human liver disease remains to be demonstrated, but it would seem to be of potential value Dr Forbes in a personal communication states that he has used xanthine in one case of phosphorus poisoning and felt that it played a great part in the patient's recovery Since it takes from 24 to 48 hours for xanthine to exert its maximum protective action, its action, if given after exposure, would be merely to help accelerate repair

OUTLINE OF TREATMENT

- 1 Remove unabsorbed carbon tetrachloride from the gastrointestinal tract by stomach lavage, and colonic irrigation
- 2 Force fluids by mouth and intravenously to dilute and wash out carbon tetrachloride and toxic products
- 3 Prevent or treat signs of intoxication and organic damage by
 - a 10 to 15 c c of 10 per cent calcium gluconate intravenously every five or six hours the first two days, then two to four times a day depending on severity
 - b Hypertonic glucose intravenously two to four times daily
 - c High carbohydrate, low fat and low protein diet
 - d 20 grains of calcium gluconate by mouth every four hours

- 4 Transfuse with blood or blood plasma if there has been much loss of blood
- 5 Repeat blood chemical determinations until blood returns to normal
- 6 Rest in bed until evidences of liver and kidney damage have disappeared

CARBON TETRACHLORIDE AS A HEALTH HAZARD

In 1933, 30,343,693 pounds of carbon tetrachloride were used in this country and in 1938, 77,975,057 pounds were used. This widespread use of carbon tetrachloride presents a definite health hazard. In industry this hazard has been recognized and largely controlled. Great industries (chemical and drug, rubber, paint, fire extinguisher, and dry cleaning), in which this substance is used extensively, have studied the problem and have taken steps to protect workers from acute and chronic poisoning. Investigations by Smyth and Smyth,¹⁷ Davis,¹⁸ and others interested in industrial medicine illustrate the type of research responsible for these improved conditions. Smyth¹⁹ pointed out that considering the enormous quantity of carbon tetrachloride used in industry there have been surprisingly few casualties. He bases his opinion partly on the small number of cases reported in the literature and partly on reports from insurance companies, health departments and departments of labor and industry. He could find only 122 acute and subacute cases reported, 27 of these being fatal. Of the 27 fatal cases, 14 were due to the use of carbon tetrachloride as an anthelmintic. Semetra,¹⁰ in 1939, collected a series of 141 cases, 39 of them fatal. Cases reported in the literature probably represent only a small percentage of the total cases occurring. Carbon tetrachloride poisoning is not a disease reportable to health departments, and cases dying a few days after poisoning may have been recorded as acute hepatitis or acute nephritis, without mention of carbon tetrachloride. In fact, in some instances it may not have been known that carbon tetrachloride was the offending agent because the label on the container made no mention of the contents. In reviewing the case reports, but few acute cases occurred in industrial plants, which proves that care and education of workers have reduced the risk where its use is supervised.

In medicine carbon tetrachloride is used internally only as an anthelmintic, principally in the treatment of hookworm, and externally to cleanse the skin. If the patient is properly prepared before the drug is administered and it is given on an empty stomach there is little risk in using it.

In nearly every home can be found a can or bottle containing one of the many brands of cleaning fluid containing carbon tetrachloride. Thousands of small clothes cleaning, and hat and shoe cleaning establishments use carbon tetrachloride daily; many of the users do not know what they are using and use it carelessly. One large New York department store sells 11 different brands of cleaning fluid containing carbon tetrachloride. Our neighborhood drugstore sells five.

The Federal Security Agency, Food and Drug Administration, states that there is no federal law which specifically requires warnings to appear on the labeling of products of this type. The Federal Food, Drug and Cosmetic Act does not regulate cleaning fluids other than those considered cosmetics. Section 502 requires the proper labeling of "drugs or devices" but cleaning fluids are apparently not so considered.

It is the custom of many of the manufacturers of these products to include a warning on the label to the effect that it should be used in a well ventilated room or near an open window. The character and presence of a warning seem to be at the discretion of the producer rather than dictated by law.

Is this type of warning sufficient? The warning usually appears in small print inconspicuously placed on the label. In fact, statements as to the safety of the product, because of its non-inflammable nature, are often emphasized giving a sense of false security. One product seen in a small hat cleaning establishment had this notice printed in large type on the front of the container—"Non-Explosive, contains no acid. Safe for fabric. Safe for you. Here at last a real spot remover!" On the side of this container, at the bottom of the instructions as to its various uses, in the same sized small type, appears the following "Volatile solvent. Use with adequate ventilation. Avoid prolonged breathing of vapor." The proprietor of this shop said he had never seen this warning or known that it contained a poisonous substance and had, on occasions, noticed that he became light-headed and had a headache after using it. Daily exposure of this nature may cause chronic liver damage.

If an adequate, conspicuously placed warning to the effect that the fluid is poisonous if inhaled or drunk were placed on the container it would be used with greater care and kept in a safe place. In the first case here reported, if the parents had appreciated the nature of the cleaning fluid it would not have been left in an accessible place within easy reach of a curious child, and in the second case the fluid would not have been carelessly poured into a whiskey bottle which still bore the whiskey label. Nearly every case reported in the literature could have been prevented if the purchaser had appreciated the fact that the product was poisonous. The following excerpts from case reports illustrate this. School janitor died in four days of liver symptoms after applying floor wax, maid cleaning dress in cleaning fluid found dead beside basin, man cleaning old telephones became sick, man drank fluid by mistake and died, woman overcome washing hair, man overcome spraying room with cleaning fluid, man painting brewery vat with preparation containing carbon tetrachloride, two year old boy swallowed fluid, woman cleaning dress in closed room, man cleaning furniture and draperies, dry cleaner overcome, three negroes drank cleaning fluid from can on garbage dump—all died, five sailors overcome by fumes moving tins in store room, three students ill after cleaning ink pads on printing press.

It would not be necessary to frighten the buyer by requiring a skull and crossbones type of label, but an adequate warning could be prescribed by law which would not interfere with the sale of this useful product, but would be fair to both buyer and seller. The contents of the product should be stated on the label.¹ Public health education by our health departments and those interested in preventing disease is worth consideration. Use of carbon tetrachloride in industry is being made safer through education and protective devices. Proper labeling and education can render the same degree of protection to all users, for it is definitely a preventable disease.

An editorial in the *Journal of the American Medical Association*²⁰ entitled "Volatile Poisons in the American Home" stresses the importance of this type of health hazard and warns against the careless use of such substances. The fact that carbon tetrachloride masquerades under a host of trade names without its presence being indicated is responsible for many mishaps.

CARBON TETRACHLORIDE POISONING A DISEASE ENTITY

In treating unusual diseases with which the physician is not familiar, two procedures are open to him, to turn to books and read up the subject, or to seek help from someone who is familiar with it. Both procedures were resorted to in our first case. In no accessible textbook could any useful information be found. Two consultants were called and considerable difficulty was encountered in finding someone familiar with this condition. It is evident from the case reports in the literature that in many cases the essential procedures of proper treatment were not applied.

In reviewing many of the latest editions of our standard textbooks of medicine, therapeutics and toxicology, not one was found which described carbon tetrachloride poisoning as a disease entity. Carbon monoxide, phosphorus and bichloride of mercury poisoning were so considered but not carbon tetrachloride. The symptomatology, pathology and treatment of this poisoning are definite and its incidence sufficient to warrant its recognition. The writers of textbooks should include carbon tetrachloride poisoning in the table of contents.

SUMMARY

1 Two cases of acute carbon tetrachloride poisoning have been presented. The first, a nine year old boy receiving a large dose by inhalation showed evidence of liver and kidney damage, followed by a slow convalescence. The second, a 48 year old man, an alcoholic, after drinking cleaning fluid died after 10 days' illness during which he presented symptoms and signs of extensive damage to the liver, kidneys and gastrointestinal tract. An autopsy confirmed these findings.

2 The treatment of this condition is discussed, especially the importance

of immediate and continued administration of calcium and glucose until evidences of intoxication and organic damage have disappeared

3 That carbon tetrachloride poisoning presents a definite health hazard is demonstrated. Laws requiring the proper labeling of products containing carbon tetrachloride are urged, and education of its users is suggested

4 A plea is made to the writers of textbooks to consider carbon tetrachloride poisoning a disease entity, thus making knowledge of its nature and treatment accessible

BIBLIOGRAPHY

- 1 LAMSON, P D, MINOT, A S, and ROBBINS, B H. Prevention and treatment of carbon tetrachloride intoxication, *Jr Am Med Assoc*, 1928, **xc**, 345-349
- 2 WOLFE, F. Effect of calcium administration on carbon tetrachloride toxicity in mice, *Quart Jr Pharm and Pharmacol*, 1933, **vi**, 413-417
- 3 CUTLER, J T. The influence of diet on carbon tetrachloride poisoning in dogs, *Jr Pharmacol and Exper Therap*, 1932, **xlv**, 209-226
- 4 MINOT, A S. Mechanism of hypoglycemia produced by guanidine and carbon tetrachloride poisoning, *Jr Pharmacol and Exper Therap*, 1931, **xlvi**, 295-313
- 5 BOLLMAN, J L, and MANN, F C. Experimentally produced lesions of the liver, *ANN INT MED*, 1931, **v**, 699-712
- 6 LACQUET, A M. Experimental pathology of the liver: effects of carbon tetrachloride on normal and on restored liver after hepatectomy, *Arch Path*, 1932, **xliv**, 164-176
- 7 CAMFRED, R, and KARUNARATNE, W A E. Carbon tetrachloride cirrhosis in relation to liver regeneration, *Jr Path and Bact*, 1936, **xlvi**, 1-21
- 8 PEERY, T M. A study of carbon tetrachloride poisoning: stages of hepatic damage and repair in man, *Arch Path*, 1938, **xlvi**, 923-941
- 9 FRANCO, S. Nephritic syndromes caused by industrial poisoning with carbon tetrachloride, *New York State Jr Med*, 1936, **xxxvi**, 1847-1853
- 10 SFUETRA, H. Nephrosis due to carbon tetrachloride, *Arch Int Med*, 1939, **lxiii**, 760-777
- 11 FORBES, J C, and NEALE, R C. A new preparation protecting against rat liver necrosis, *Proc Soc Exper Biol and Med*, 1936, **xxiv**, 319-320
- 12 FORBES, J C. Studies on the prevention of liver cirrhosis by the sub-cutaneous injections of xanthine containing preparations, *Jr Pharmacol and Exper Therap*, 1939, **lxv**, 287-293
- 13 NEALE, R C, and WINTER, H C. Identification of active crystalline substance from liver which protects against liver damage due to chloroform or carbon tetrachloride. Study of related compounds, *Jr Pharmacol and Exper Therap*, 1938, **lxii**, 127-148
- 14 FORBES, J C, and outhouse, E L. Studies on the mechanism of the protective action of xanthine against carbon tetrachloride poisoning, *Jr Pharmacol and Exper Therap*, 1940, **lxviii**, 185-193
- 15 BARRETT, H M, MACLEAN, D L, and MCHENRY, E W. Experiments with an "anti-narcotic" material prepared from liver, *Jr Pharmacol and Exper Therap*, 1938, **lxiv**, 131-137
- 16 FITZHUGH, O G. Liver regeneration in rats, protected with xanthine against carbon tetrachloride poisoning, *Proc Soc Exper Biol and Med*, 1939, **xl**, 11-15
- 17 SMYTH, H F, and SMYTH, H F, JR. Safe practices in the industrial use of carbon tetrachloride, *Jr Am Med Assoc*, 1936, **cvii**, 1683-1687
- 18 DAVIS, P A. Carbon tetrachloride as an industrial hazard, *Jr Am Med Assoc*, 1934, **ciii**, 962-966
- 19 SMYTH, H F. Carbon tetrachloride in industry, *Indust Med*, 1935, **iv**, 12-15
- 20 Volatile poisons in the American home. Editorial, *Jr Am Med Assoc*, 1933, **ci**, 1238-1239

A THEORY CONCERNING THE MANNER IN WHICH THE STOMACH EMPTIES ITSELF*

By WILLIAM TRAVIS GIBB, JR., M.D., F.A.C.P., *New York, N. Y.*

THE actual mechanics of how the stomach empties have never been explained in a perfectly clear fashion. The descriptions of this important function vary considerably in every textbook on physiology, and appear to be vague and incomplete. Cannon believes that the acidity of the chyme controls the pyloric sphincter, that a certain degree of acidity in the stomach causes it to open, and that increased acidity in the duodenum causes it to empty. There is also another factor which comes into play, namely, that mechanical stimulation on the stomach side causes the pylorus to open and that mechanical stimulation on the duodenal side causes it to close, and that as long as material stays in the cap the pylorus remains closed. The peristaltic waves tend to vary in intensity, and when a strong wave passes over the antrum it tends to open the cap and to raise the pressure in the antrum so that some of the contents of the stomach will pass through the pylorus into the antrum. Before the wave reaches the pylorus it closes. Towards the end of digestion the tone of the sphincter tends to diminish, and the pylorus relaxes so that regurgitation of food from the duodenum to the stomach occurs.

Cole, basing his conclusions upon serial radiography, states that the activity of the sphincter is directly proportional to the magnitude of the antral contractions, and that chyme passes into the duodenum during each of these contractions but not during the intervals.

Wheelon and Thomas claim that, when a peristaltic wave beginning in the body of the stomach reaches the antrum, the sphincter becomes relaxed, and that material swept forward by the constricting wave is free to pass through the opening of the pylorus. The pylorus closes before the wave reaches it and then there is a period in which the antrum and the pylorus are in a contracted state. After this the antrum goes into a negative phase and the pylorus remains in a contracted state.

William Beaumont and later Hofmeister and Schurtz were of the opinion that after a peristaltic wave had passed down the body of the stomach and reached the antrum it became systolic in character, almost dividing the stomach into two halves, the lower part of the wave passing onward to the pylorus.

Starling stated that there is a strong transverse band demarcating the body of the stomach from the antrum. Strong contraction waves in the

* Read before the Summit (N. J.) Medical Society, Oct. 29, 1940.

Read before the Monthly Gastro-Intestinal Conference of St. Luke's Hospital, December, 1940.

Received for publication February 25, 1941.

antrum force food toward the pylorus which remains closed, therefore the food can not escape and is forced backward forming an axial reflux stream toward the cardia, which condition permits of thorough mixing. Transitory opening of the pylorus allows a few cubic centimeters of material to be squeezed into the duodenum. Tonic contractions in the fundus produce a steady pressure. The pylorus opens more and more frequently as digestion progresses and the stomach becomes empty.

Howell says that the pylorus relaxes occasionally to allow a contraction wave to eject food into the antrum. This does not occur with each wave.

Wright adds that when empty the walls of the stomach are in rather firm apposition, but when food enters through the cardia the muscle fibers elongate sufficiently to make the cavity conform to the size of its contents. This does not change the internal pressure on the contents to any great extent. A peristaltic wave occurs about every twenty seconds. When the stomach is first filled the pylorus is tonically contracted. In three to twelve minutes the pylorus opens to permit a small quantity of chyme to escape. The pylorus relaxes and opens when a wave reaches the antrum.

Very little is said in the literature concerning the effect of gravity upon the emptying of the stomach, and this force we feel has little, if any, effect. If we take other organs of the body for analogy we find that there is not one that depends upon this force for its proper function. Certainly other parts of the digestive tract seem to operate in any position. The position of the body does not seem to have any effect upon the manner in which the stomach empties itself, for the function goes on just as well in an erect as in a horizontal position, and if horizontal, it makes no difference whether the individual be upon his side, his back or his face. This is true in spite of the fact that the filled stomach changes position to a great extent depending upon what position the body happens to be in and what media fill its lumen. The cardia is fixed, but the pyloric end is fairly movable. When lying upon the left side the pylorus may be to the left of the midline, and when on the right side may be well over on the right side of the abdominal cavity. Even when a person has the foot of his bed elevated on shock blocks, his stomach seems to empty in a satisfactory fashion. Of course one cannot say dogmatically that gravity plays no part whatsoever, certain positions may make emptying a little easier, but the evidence to back up this supposition is very sparse.

Anyone who has watched a stomach filled with a liquid barium medium under a fluoroscope could not have failed to notice that even though there was good, active peristalsis in the antrum, the cap filled only on occasion, and that it was practically impossible to fill the cap by manual manipulation until the stomach was "good and ready." If the stomach is observed patiently over a considerable period at one examination it will be noticed that the peristaltic waves start in the upper portion of the body, are shallow, sluggish and without much force. These waves travel in a caudad direction at the rate of

about one every twenty seconds. When they reach the *incisura angularis*, that is, the beginning of the antrum, they suddenly become deep and forceful and continue toward the pylorus with great regularity, taking about ten seconds to traverse this distance. As the observer watches these waves he will note that suddenly, for no appreciable reason, the antrum takes on a firm, ball-like appearance, and that it is completely divided from the fundus except for perhaps a trickle of barium. This ball seems to contract to a slight degree and as it does so the cap fills and barium is seen to literally shoot through the entire duodenum to the first part of the jejunum. This is best observed at the beginning of the examination, the first time it happens, when the duodenum is empty. After that there is barium scattered throughout the duodenum and this phenomenon is not so apparent. As this occurs the usual peristaltic wave begins just distal to the *incisura angularis* and travels toward the pylorus in the usual fashion. The wave seems a little deeper than usual but this may be only apparent due to the increased tonicity of the antrum. The initial division at the *incisura* relaxes when the wave is under way. The cap is distended during this first rush of contents into the duodenum and remains so for a comparatively short while. It then takes on a smaller diameter. Peristalsis in the duodenum seems to start just distal to the cap.

This course of events gives one the impression that the material from the stomach is being ejected in a forceful fashion, much more strongly than would be expected from a peristaltic wave travelling at the rate of one centimeter a second. I do not think that a peristaltic wave travelling at this rate of speed, unless it actually occludes the lumen of the hollow structure over which it is travelling, can apply much pressure to the watery contents ahead of it. The old analogy of the sausage skin filled with sausage meat does not apply in this case. In this demonstration the fingers are so placed around the tube as to simulate a constriction band, and then as they are moved along slowly the contents of the tube are forced out ahead of it. This analogy might be true if the contents of the antrum were a semi-solid, as is the sausage meat, but they are not, they are to all intents a liquid. If you repeated this experiment filling the tube with water, very little increase in pressure would be obtained so long as the rate of travel of the constriction band remained slow (one cm. a second), and the lumen of the tube was not entirely constricted. If, however, simulating a rush wave in the intestinal tract, you moved your constricting band forward at a rapid rate, you would push the water ahead of the band in an excellent fashion. Also if you entirely occluded the lumen of the tube with your constricting band, water would be forced out ahead of the band. This is one small piece of evidence that makes us feel that there is more to emptying the stomach than a mere peristaltic wave. What evidence there is points to the fact that the peristaltic waves in the antrum do not entirely occlude the lumen. It might be argued that these waves set up currents in the liquid and that these cur-

ients all tend to go toward the pylorus. However, these currents, of necessity, must be weak and could not produce the rapid ejection of fluid into the duodenum that we have noted.

By means of the gastroscope* a new structure in the stomach has been described by many observers, namely the *musculus sphincter antri*. This structure is a rope-like ridge located upon the greater curvature at right angles to the long axis of the stomach, just opposite to the *incisura angularis*, and it extends about half way upward on the anterior and posterior walls. Although it is seen without exception in every stomach and constitutes part of the first landmark that is used for purposes of orientation, it varies somewhat in each individual, being more pronounced in some and less so in others. It seems to consist of a ridge of muscle covered with normal mucous membrane and derives its rope-like quality from the fact its axis is not quite at right angles to the usual mucosal folds. These folds, which run longitudinally to the long axis of the stomach, traverse the *musculus* at a slightly oblique angle. The *musculus* is not found at post mortem, in the dissecting room or at the time that the stomach is open in the operating room. It does not seem to be differentiated from the rest of the stomach wall histologically. Therefore it would seem that it is physiological or functional in character, that it is a functional structure and has some definite use in the mechanics of the stomach. It is there for a purpose, for if it were vestigial it would probably have long since disappeared. Only once has it been described except in connection with gastrosopic observations, and that was in Germany when two men, who had been electrocuted, were examined at necropsy a few moments after death. Many times during our gastrosopic examinations a spasm has been noted which for the time being impeded the examination of the antral portion of the stomach. These spasms have always caused complete contraction of the lumen of the stomach and have involved this structure, namely the *musculus sphincter antri*. The contracted lumen of the stomach at this point usually has a slit-like appearance rather than a stellate one. The contracted portion of the walls seems to involve the greater curvature and part of the anterior and posterior walls, and not the lesser curvature. We have noted this stricture or spasm on several occasions when we were examining individuals with thin abdominal walls. In such people, when the scope is in place and the examining room very dark, the outlines of the stomach can be seen through the abdominal wall perfectly. When the spasm was noted by the observer at the eye-piece, it was seen that the transilluminated image of the stomach on the abdominal wall had the lower portion cut off, but when the gastroscopist announced that the spasm was relaxed the remaining portion of the stomach was suddenly illuminated suggesting that the antrum had been dis-

*The personal observations herein mentioned were made at St Luke's Hospital and Knickerbocker Hospital, New York City, in connection with the use of the Wolf-Schindler Flexible Gastroscope in over 750 examinations of the stomach. This work was done between February 1938 and September 1940.

tended at the time of the spasm and that the spasm merely divided the stomach into two portions. It would seem from these observations that the *musculus sphincter antri* had the function of forcibly dividing the stomach into two portions. I say forcibly because the spasm cannot be relieved by distending the stomach with air under some pressure.

The gastroscope has been extremely useful in establishing another fact. In over 700 observations we have seen the pylorus, either in whole or in part, more than 80 per cent of the time. Not once have we seen a pylorus that was not patent. This structure remains open practically all of the time and closes only for a brief interval when the contraction wave from the antrum reaches and blends with it. This has been consistently true and not one exception has been noted, although several times we have noted a pylorus that did not close at all during the examination. In these cases no contraction waves were seen in the antrum. This observation has been so consistent and so uniform that we have felt that it must represent the usual rhythm of the pylorus. In several instances we have examined stomachs that contained a considerable quantity of food. The deep contraction wave can be seen starting in the first portion of the antrum just distal to the *musculus sphincter antri*. It progresses slowly and evenly, as a ring around the antrum, all portions of it reaching the pylorus at the same time. Just as it reaches this structure and blends with it the pylorus closes. It remains closed for about one second and then opens again. The closure of the pylorus does not as a rule take place in a stellate fashion as has been described and pictured in certain books on gastroscopy, that is, with radial folds of mucosa extending from the closed orifice as is the case with the anus. Rather, the tightly closed pylorus might be said to resemble a full blown rose, that is, there is a reflux of loose mucosal folds back toward the stomach, each fold representing the petal of the rose. This is a rather unusual appearing phenomenon, and one difficult to describe, but we feel that it is the usual course of events and that any deviation from it is abnormal. In certain prepyloric lesions we have noted the stellate type of closure. However, the full significance of variations from what we consider normal has not been arrived at. It is interesting to note here that even though we have examined over 20 stomachs in which there were varying degrees of food retention we have never seen a single pylorus that was not fully patent. In one of these, however, there was some evidence of cicatrization as shown by an elliptical shaped pyloric orifice which had no apparent reduction in the area of the lumen. In some of these cases of retention the peristaltic waves were very shallow, or even absent. In the latter cases the pylorus did not close during the period of observation.

There is still another curious fact which has been observed on numerous occasions, particularly in reference to the use of the flexible gastroscope, but which has not been commented upon nor for which has any explanation been vouchsafed. In order to distend the walls of the stomach so that a

view of them can be obtained, air is pumped into the stomach. This is done by means of a small hand bulb similar to that used in connection with the sigmoidoscope. In a normal stomach the air stays in place once the proper degree of distention has been obtained and none has to be added during the course of the examination. However, in stomachs in which a gastroenterostomy has been performed the air leaks out, particularly at the beginning of the examination, and has to be replaced constantly. The air must escape into the jejunum for it does not come out of the cardia and esophagus. This indicates that there is some mechanism in the duodenum which prevents the passage of air from the stomach through the pylorus, which we have already noted is open practically all of the time.

Thomas and Morgan have noted that as a peristaltic wave approaches the pylorus there is a marked inhibition of the rhythmic contractions of the first part of the duodenum, and that recovery of the normal tone and peristaltic activity of the duodenum takes place when the pylorus closes. Could it not be a fact that the tone of the duodenum varies? That when the stomach is ready to eject material into the duodenum, its tone diminishes so that it can dilate sufficiently to conform with the bulk of this ejected material? Between these periods the tone is so increased as to be able to withstand the usual slight variations of pressure within the stomach due to peristalsis. This apparent contraction of the walls of the duodenum is what keeps the air within the stomach during the gastrosopic examination. In the case of the stomach with the gastroenterostomy opening, the jejunum has none of these qualities of increased and decreased tone and so there is no barrier to the passage of air into and along its lumen. Of course there is a limit to the volume of air that can be forced into the jejunum at the mild pressure used in inflating the stomach, and after this volume has been reached the back pressure equals the pressure within the stomach and no further leakage occurs.

From these foregoing observations we have deduced that there must be some very definite mechanism not previously described that enables the stomach to empty itself. This mechanism must be different from what has been described heretofore, for these facts seem very evident and positive, and they do not fit exactly into any previous explanation. It can be argued that a stomach filled with air or with the usual barium meal does not behave in the same fashion as one filled with the usual types of food. This is true, but it is also true that these facts have been observed with very great regularity, signifying to us that there must be some underlying mechanism which is very definitely established and which must serve some function. The following is a theory based upon these observations.

The stomach is divided into three portions: the antrum, the body and the fundus. The antrum is that portion which lies distal to the *incisura angularis* and the *musculus sphincter antri*, the body is the remaining portion except for that part which is above the cardia which is called the fundus. This latter portion contains the air bubble. When empty the walls of the

stomach lie in close apposition. This approximation of the walls must be forceful at times, for we have noted in certain individuals that the barium meal collects for a time in the fundus and that gradually a trickle of it filters down through the body to the antrum. This apparent spasm persists over a considerable period at times. Normally, however, the walls of the stomach enlarge enough to accommodate the amount of material that is placed inside of it and there is not any increase in pressure within the stomach due to stretching or contraction of the walls. When filled with food the body of the stomach acts as a reservoir, in which the food is retained and gently mixed and agitated by the shallow peristaltic waves which start in its upper portion and progress in a caudad direction. If the stomach is carefully observed over a considerable period, waves can be seen going in an opposite direction. These are apparently normal according to Alvarez. Here the hydrochloric acid and other juices are mixed with the food and some of the changes take place which prepare the ingested material for future digestion. Other factors probably help in this mixing process—the musculature of the abdominal wall for one. Normally these muscles are contracting and relaxing frequently, which in turn must exert some alternating pressure and relaxation upon the filled stomach. The movements of respiration, that is contraction and relaxation of the diaphragm and the accessory movements of the abdominal muscles must affect the stomach as well. All these factors assist in bringing the contents of the body down to the antral region.

When the food material is in the antrum it is further kneaded by the far more powerful contraction waves found here. Probably certain currents are set up which bring the food best prepared at the time to the region of the pylorus. When the duodenum is ready to receive some of the contents of the stomach, or when the contents of the stomach are in the proper state for passage to the duodenum, or when both of these factors are favorable, there is a contraction of the *musculus sphincter antri* which divides the stomach into two distinct compartments. This contraction must of necessity involve a fairly large mass of muscle which shortens the antrum and when the closure is complete raises the hydrostatic pressure of the antral contents. There is also at this time what might be termed a systole of the antrum, that is, the muscle of the antrum contracts and exerts still more hydrostatic pressure. As we have stated, the pylorus is open at practically all times. It being open, and the junction of the body and antrum of the stomach closed, the liquid food is literally squirted into the duodenum and cap under considerable pressure. That this is probably true is evident when we remember how rapidly under the fluoroscope, the barium mixture enters the duodenum and how far it travels before reaching a stop. Shortly after this so-called systole starts, the usual contraction wave starts just distal to the *musculus sphincter antri*. This wave is probably no deeper than usual, but appears to be so because the antrum is in a hypertonic state. Once the wave starts the constriction of the *musculus* begins to relax, but the flow of the liquid is already under way and much of the duodenum is filled, so that the

wave tends to keep the current of the liquid going in the same direction, even though the pressure from the systole is relieved. The principal work has been done by the systole, and the contraction wave keeps going what was already set in motion. When the wave arrives at the sphincter, the pylorus closes and reflux is prevented. Apparently the only function of the pylorus is to prevent reflux.

The cap and the duodenum are filled under a certain amount of positive pressure and the cap acts as a pressure regulator. Its musculature is thinner than the rest of the duodenum and it has more expansile qualities. It is filled with the first rush of liquid, expands to its limit, thereby taking up the momentary excess of liquid and acts as a reservoir. With the closure of the pylorus the cap tends to partially empty itself, passing on its contents to the duodenum. In this way we have a mechanism which tends to keep a constant pressure within the duodenum, so that this portion of the gastrointestinal tract is not subject to variation in pressure that would be present if the stomach contents were ejected suddenly into it. This function might be compared to the expansile qualities of the aorta, which by expanding with each systole of the heart, tends to equalize the pressure in the systemic circulation. When the pylorus again opens the hydraulic pressures within the stomach and duodenum are equalized, and when the duodenum is again ready to receive more material the process is repeated.

We have postulated that there is a variation in the tone and peristalsis in the duodenum. When the duodenum is ready to receive some of the stomach contents its tone decreases and its peristalsis is slowed up. This is probably coincidental with the initiation of the systole of the antrum. When the systole is completed the tone is raised in the first portion of the duodenum, the walls are in apposition again and cannot be parted by the usual pressures within the stomach. This produces an effective division between the duodenum and the antrum and prevents an appreciable exchange of material between the two until the duodenum is again ready to receive more food.

This whole course of events is particularly applicable during the earlier part of gastric digestion, when the stomach is more or less completely filled. Inasmuch as the pylorus remains open practically all of the time there must be some slight exchange of contents between these systolic cycles. We do not claim that there is only one way in which food gets from the stomach to the duodenum. The usual peristaltic waves probably convey some material into the duodenum, particularly during the latter part of the time when the stomach contains food. Also there is a reflux of small quantities of material from the duodenum, especially at the end of the gastric digestive period. How the impulse is initiated by the duodenum when it is ready to receive more food, is difficult to determine and does not really concern us in this paper. It may be merely a matter of differences in pressure, when the duodenum is empty, when the pressure is lower than it is in the stomach,

the systole is instigated. It is not a matter of acidity and alkalinity for it has been observed many times that a stomach, in which there was no demonstrable acid, emptied just as well as one which was normal in this respect.

The reason for gastric retention—why some stomachs are slow in emptying or do not empty themselves entirely—requires an explanation. As we have said, at no time have we ever seen a pylorus that was not patent. We have never seen anything that suggested a spasm or a cicatricial closure. The reason for non-emptying must lie in mechanisms not as simple as mere stenosis. Certain types of retention might be explained upon the basis of atonic musculature of the stomach wall—that the musculature did not have enough tone to produce an actual systole, and that whatever emptying occurred was due to the usual antral peristalsis. This would indeed slow the process up considerably, if not actually prevent it. In other types of retention the difficulty may lie on the duodenal side of the pylorus. It is being recognized that duodenitis is a more common condition than was previously suspected. If a duodenum was acutely inflamed, its normal gradient would be disturbed and raised. This could delay or interfere with the emptying of the duodenum and therefore delay its preparation for the reception of stomach contents. Then again perhaps there might be some functional disturbance of the variations in tone of the first portion of the duodenum, so that the general tone was raised and during the relaxed phase, the relaxation was not complete enough to allow much food to enter during systole. Or perhaps the intervals between the relaxed phases are increased in duration and the systolic phase in the antrum occurs with decreased frequency. In all events there are probably a number of different reasons for gastric retention. Clinically we know that some types clear up with rest in bed and adequate medical treatment but tend to recur, and that other varieties do not improve under this regime and surgery has to be resorted to in order to effect a cure.

We present this theory, knowing full well that the chain of evidence lacks many links. The direct experimental proof of such a theory would require apparatus of greater delicacy than is now available, as well as development of special techniques. For instance, to prove that during the systolic period of the antrum there was an increase in hydraulic pressure in this part as compared with the body of the stomach would require something far more delicate than the double balloon apparatus. The variations in pressure of necessity must be comparatively small, and the limits of error of such an apparatus are far too large to make it of any use.

In summary we present a theory to explain the course of events that takes place during the emptying of the stomach. This theory includes only the mechanics and hydrodynamics involved. The *musculus sphincter antri* contracts, forcibly dividing the stomach completely into two compartments. As this occurs there is an increase in tone of the antrum, which applies equal pressure upon its contents, forcing them through the pylorus under some

pressure The usual peristaltic wave then passes over the antrum and when it reaches the pylorus and blends with it, the pylorus closes and remains so for only about one second The first portion of the duodenum exhibits increased tone except during this cycle when the tone decreases

BIBLIOGRAPHY

- 1 WRIGHT, SAMSON Applied physiology, 6th Ed , page 554
- 2 HOWELL, WILLIAM H Text book of physiology, 12th Ed , page 758
- 3 STARLING Principles of human physiology, 6th Ed , page 579
- 4 McLEOD Physiology in modern medicine, 8th Ed , page 665
- 5 ALVAREZ, WALTER Mechanics of the digestive tract, 2nd Ed , 1928
- 6 BEST and TAYLOR Physiological basis of medical practice, 2nd Ed , 1940
7. THOMAS and MORGAN A study of reflexes involving the pyloric sphincter and antrum, Am Jr. Physiol , 1934, cviii, 683
- 8 COLE, L G Value of serial radiography in gastrointestinal diagnosis, Jr Am Med Assoc , 1912, lix, 1947
- 9 EUSTERMANN and BALFOUR Stomach and duodenum, 1st Ed , 1936

- 7 Many factors influencing the water balance of the body
- 8 The sensitivity of various reflexes having their origin in the pulmonary and pulmonary vascular tissues
- 9 The rate at which the accumulation takes place

Accepting all these variables we may inspect some of the direct consequences of isolated left ventricle failure. They may be considered in two groups: those associated with the heart itself and those manifest in other parts of the body.

A Manifestations associated with the heart itself

1 The dilatation of the ventricle is usually demonstrable by roentgen-ray, and Weiss and Robb² were able to show that with this dilatation there is often a reduction in the excursion of the ventricle's shadow. This was true in patients who had little or no diminution in cardiac output.

2 *Pulsus alternans* appears to be associated with a change in function of the left ventricle which often precedes failure. When it occurs without tachycardia it should be interpreted as a warning signpost, suggesting left ventricle weakness and perhaps failure not far behind.

3 No arrhythmia is predominantly associated with left ventricular failure, but the onset of auricular fibrillation occurs not rarely in some relation to the development of left ventricular failure. When this occurs it is usually considered that the auricular fibrillation, by bringing about a rapid ventricular rate, is itself a precipitating cause of the failure. This is certainly so in some instances, but the cart and the horse may be turned around in others. It has been suggested by Brill and Meissner⁶ that the distention of the left auricle resulting from left ventricular failure may be a factor in the initiation of auricular fibrillation. They point out that auricular fibrillation occurs most frequently in those conditions (mitral stenosis or failure of the left ventricle) in which the left auricular pressure is elevated. But most patients with left ventricular failure have a normal rhythm.

4. Left ventricular failure is frequently associated with a *gallop rhythm*, usually a mid- or protodiastolic type. It is usually considered that such a phenomenon is brought about by rapid ventricular filling, and that it thus may be a manifestation of an abnormally great difference in pressure as between auricle and ventricle.

Certain observations, recently made in my laboratory by Swank, Porter and Ycomans,⁷ illuminate several aspects of the problems of failure of the left ventricle and may be presented here. These workers studied the effects upon certain circulatory functions of the intravenous infusion of fluid. They found, as others have done, that when saline solution, glucose solution, or blood were introduced in amounts which caused increase in the total blood volume of 50 per cent or more, many of the phenomena of congestive heart failure were reproduced. The phenomena so induced include dilatation of the heart, systolic murmurs, elevation of the venous pressures in lung and

in periphery, gallop rhythm, congestion of lungs and liver, and (in some animals) edema of the lungs. These phenomena occurred at a time when the cardiac output and the blood supply to the tissues were above the basal level. It may be debated (fruitlessly, I think) whether these animals had heart failure or not, but in any event the experiment permits us to study some phenomena often a part of what we call failure.

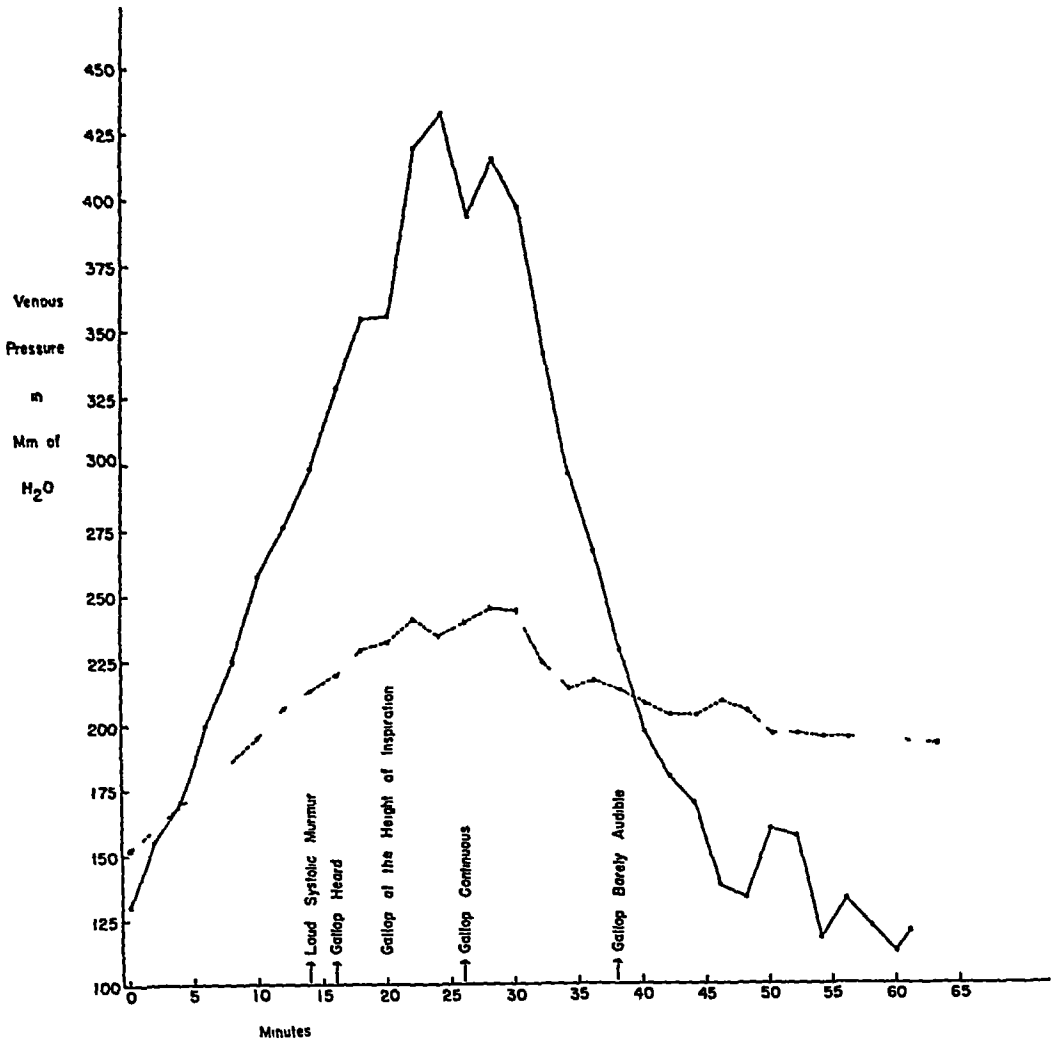


FIG 1 The left auricular pressure (solid line) and the peripheral venous pressure (broken line) during infusion. The zero point of the manometers was at the level of the skin of the dog's back. The infusion was stopped after 30 minutes.

Figure 1 records the peripheral venous pressure and the left auricular pressure in a dog subjected to such an injection. This animal was anesthetized with alpha-chloralose. The injected fluid was normal saline and was put into a femoral vein at the rate of 2.7 c.c. per kilogram per minute for 30 minutes. Thus a 24 kg. dog received a total of 1944 c.c. in 30 minutes. There is a rise in the venous pressure of both circuits beginning immediately

after the onset of the injection, the pulmonary venous pressure rises more rapidly, in this animal, than the peripheral and reaches a maximum height of 433 mm, while the systemic venous pressure goes only to 240 mm. After cessation of injection the pressure falls rapidly in both circuits and within 15 minutes is approaching normal. The interest of this chart is that during the injection certain new signs appeared. When the left auricular pressure reached 329 mm of water a gallop rhythm was heard, when the pressure had fallen to 198 mm it was no longer audible. A systolic murmur also came and went with a series of events which may have been expected to dilate the mitral ring.

Further evidence that the basis of gallop rhythm is to be found in an elevated auricular pressure is seen in some recent work of Stead and Ebert.⁸ By trapping blood in three extremities they were able to diminish the effective blood volume by some 16 per cent. In a hypertensive subject the pooling of blood in the extremities was accompanied by a disappearance of the gallop, presumably because of a lowering of left auricular pressure. When the tourniquets were released the gallop returned.

These observations seem to associate gallop rhythm with a high pressure in the left auricle. In my judgment a gallop rhythm is a useful sign because it may be a relatively early indication of rising auricular pressure, and we are probably all tardy in our recognition of left ventricular failure.

These experiments also emphasize the highly significant fact that the degree of pulmonary congestion may alter with great rapidity.

5 Wood and Selzer,⁹ working in the National Hospital for Diseases of the Heart and the British Postgraduate Medical School, have recently suggested what they think may be an electrocardiographic sign of left ventricular failure. In a recent communication they draw attention to a type of P-wave, which is wide and bifid and of low voltage, which they have found in association with left ventricular failure in hypertension and in aortic incompetence.

6 A large increase in the size of the roentgen-ray shadow of the left auricle is not frequent, according to the careful studies of Weiss and Robb.² The observation is in striking contrast to the situation in mitral stenosis, in which a marked enlargement of the left auricle's shadow is regularly observed. Most of the patients studied by Weiss and Robb had hypertension or aortic disease as the basis for their left ventricle failure. It is accepted, on the basis of wide experience, that auricular distention from mitral stenosis is of long duration as compared with that occasioned by left ventricular failure. Some recent work by Eppinger, Burwell and Gross¹⁰ has shown that the great increase in pulmonary blood flow which may occur in patients with patent ductus arteriosus may be associated with a definite increase in size of the left auricle. It may be that even a normal mitral valve is not wide enough to transmit so great a volume of blood without an elevated auricular pressure, or this picture may be due to left ventricular failure of

long standing. However that may be, the left auricle is usually dilated when the ductus arteriosus is widely patent.

B When we leave the heart itself and turn our attention to the pulmonary vascular bed we encounter manifestations at once more complex and more disquieting than those we have so far considered. We are greatly handicapped in the study of the pulmonary circulation by the lack of methods for measuring pressure in the pulmonary veins and arteries. These are no doubt as important as similar measurements in the systemic circulation but their variations are thought about much less, presumably because we cannot get precise information about them. Left ventricular failure results in an increase in the amount of blood in the lungs, as shown by many studies (Blumgart and Weiss,¹¹ Weiss and Robb²). This increase results in the diminution of air space, unless there are appropriate compensatory changes, in alterations in the consistence of lung tissue which tend to diminish its mobility, in a slowing of the movement of blood, in the opening up of new capillaries, and in an elevation of pressure in pulmonary vessels. These changes, through their mechanical and reflex effects, bring about a series of symptoms and signs, including

- 1 Prolongation of the pulmonary circulation time
- 2 Diminution of vital capacity
- 3 Dyspnea (including the paroxysmal type)
- 4 Cough
- 5 Bronchial constriction
- 6 Roentgen-ray evidence of congestion
- 7 A loud pulmonary second sound
- 8 Edema (either interstitial or alveolar)
- 9 Hemoptysis } (these are late manifestations)
- 10 Cyanosis }
- 11 Laryngeal paralysis?
- 12 Pleural effusion?

None of these manifestations is simply produced, their mechanisms are complex, and they may interact with each other to complicate matters still further. Each of them, however, may be explained primarily on the basis of accumulation of blood and pressure in the pulmonary vessels. A few examples will suffice.

1 Dyspnea, in general, as Peabody¹² showed, occurs when the actual volume of ventilation exceeds a certain (or individually uncertain) fraction of the maximum ventilation possible. Dyspnea is encouraged, therefore, by factors which either increase the ventilation or decrease the maximum ventilation possible. Harrison⁸ has illustrated the links in the chain of events leading from left ventricular failure to dyspnea, and to its paroxysmal exacerbation in an attack of cardiac asthma. It is easy to see how left ven-

tricular failure reduces the maximum ventilation, since the vital capacity is reduced by the space-occupying extra blood in the lungs, by the stiffening effect of congestion on the lung tissue, and (in some patients) by interstitial or alveolar edema. Bronchial constriction also may occur to limit ventilation. At the same time the congested lungs are the source of vigorous reflex stimulation of respiration, as was shown by Harrison³ and by Churchill and Cope¹³. Similar reflexes may be important in cough and in bronchial narrowing. It is important to remember that severe dyspnea and cardiac asthma can occur in the absence of any demonstrable edema, i.e., in the absence of râles.

Is dyspnea to be called an *early* symptom of failure of the left ventricle? It certainly is, and not very rarely the first symptom of which the patient gives an account is an attack of paroxysmal dyspnea, most often coming on at night. True, the more careful the history and the more sensitive and observant the patient the more frequently one will obtain an *earlier* history of dyspnea with exertion, but there are patients in whom severe attacks come early in failure. The observations in dogs just presented show how pulmonary congestion may occur with great rapidity if the capacity of the left heart is overtaxed.

Dyspnea is not only an early symptom of left ventricular failure, in some ways it is the key symptom. It may be dyspnea on exertion, nocturnal paroxysmal dyspnea, periodic respiration, orthopnea, or continuous dyspnea. Its severity and type are modified by many influences: the excitability of the nervous system, the chemistry of blood and tissues, the mobility of diaphragm and ribs, the size of the dead space and the metabolic rate. But the *fundamental* mechanism of dyspnea in left ventricle failure is congestion of the pulmonary vascular systems.

2 Cough is important, because it is not only an early symptom but also a form of physical work which may lead to further pulmonary congestion. Its causation is complex and it is often influenced by extracardiac factors.

3 Edema, hemoptysis, and cyanosis are on the whole late rather than early results of left ventricular failure and need only to be mentioned, although there are plenty of interesting and unsolved problems connected with them.

4 Then there are certain signs the mechanism of which is not well understood. King, Hitzig and Fishberg¹⁴ have reported three cases of recurrent laryngeal paralysis in left ventricular failure; this they ascribe to compression of the nerve by dilatation of the pulmonary artery. There is an obvious parallelism with the laryngeal symptoms of severe mitral stenosis, but the case is not clear. I am puzzled also by the relation of left-sided heart failure to pleural effusion, indeed, the whole question of the mechanism responsible for pleural effusion seems to me to need investigation.

At various points in this discussion we have touched on the similarity of the congestive phenomena of left ventricle failure to those of mitral

stenosis In my opinion it is desirable to try to differentiate between the congestion due to unchanging mechanical obstruction (as in mitral stenosis) and those due to fluctuations in the working capacity of the myocardium, as in left ventricular failure The utility of such a differentiation is, of course, to be found in the different reactions to treatment of the two groups, and in the differences in course and prognosis In the case of a permanent and unvarying obstruction, such as mitral stenosis without myocardial failure, changes in the degree of pulmonary congestion are occasioned chiefly by variations in the amount of blood flowing into the lungs When the obstacle is a failing ventricle there are two variables the amount of blood flowing into the lungs and the severity of the interference with ventricular function This double mechanism may explain the fact that rapid fluctuations in the degree of pulmonary congestion are much more frequent in patients with left ventricle failure than in those with mitral obstruction Obviously the management of failure of the left ventricle requires measures to diminish the amount of blood flowing into the lungs and measures to increase the ability of the left ventricle for effective and economical work

In conclusion I shall mention only three points for emphasis

1 Left ventricular failure is frequent and dangerous, and in its early stages is often pure (i.e., without associated failure of the right ventricle) These early stages are apt to be seen in office or out-patient department rather than in wards

2 The diagnosis of heart failure does not require high systemic venous pressure, an enlarged liver or peripheral edema It may be made on the evidence of isolated failure of the left ventricle Early evidences of such failure include gallop rhythm, diminished vital capacity, prolonged pulmonary circulation time, roentgen-ray evidence of pulmonary congestion, and sundry varieties of dyspnea

3 Our knowledge of left ventricular failure would profit greatly by the invention of a method of measuring the pulmonary arterial and venous pressures in patients by a painless, precise, and non-perilous procedure

BIBLIOGRAPHY

- 1 HOPE, JAMES A treatise on the diseases of the heart and great vessels, 1846, Philadelphia
- 2 WEISS, S, and ROBB, G P Cardiac asthma (paroxysmal cardiac dyspnea) and syndrome of left ventricular failure, Jr Am Med Assoc, 1933, c, 1841
- 3 HARRISON, T R Failure of the circulation, 1939, Williams and Wilkins Co, Baltimore
- 4 WHITE, P D Weakness and failure of the left ventricle without failure of the right ventricle, Jr Am Med Assoc, 1933, c, 1993
- 5 HITZIG, W M, KING, F H, and FISHBERG, A M Circulation time in failure of the left side of the heart, Arch Int Med, 1935, lv, 112
- 6 BRILL, I C, and MEISSNER, W A The rôle of coronary artery disease in the etiology of auricular fibrillation, ANN INT MED, 1941, xiv, 1341
- 7 YEOMANS, A, PORTER, R R, and SWANK, R L Observations on certain manifestations of circulatory congestion produced in dogs by rapid infusion B Results in normal dogs, To be published

- 8 STEAD, E A , JR, and EBERT, R V The action of paredrinol after induction of hemorrhage and circulatory collapse, *Am Jr Med Sci* , 1941, cci, 396
- 9 WOOD, P , and SELZER, A A new sign of left ventricular failure, *Brit Heart Jr* , 1939, 1, 81
- 10 EPPINGER, E C , BURWELL, C S , and GROSS, R E The effects of the patent ductus arteriosus on the circulation, *Jr Clin Invest* , 1941, xx, 127
- 11 BIUMGART, H L , and WEISS, S The pulmonary circulation time, the velocity of venous blood flow to the heart, and related aspects of the circulation in patients with cardiovascular disease, *Jr Clin Invest* , 1928, v, 343
- 12 PEABODY, F W Cardiac dyspnea, *The Harvey Lectures*, Series 12, 1916-1917, p 248
- 13 CHURCHILL, E D and COPP, O The rapid shallow breathing resulting from pulmonary congestion and edema, *Jr Exper Med* , 1929, xlix, 531
- 14 KING, F H , HITZIG, W M , and FISHBERG, A M Recurrent laryngeal paralysis in left ventricular failure, *Am Jr Med Sci* , 1934, clxxviii, 691

THE CRUVEILHIER-BAUMGARTEN SYNDROME; REVIEW OF THE LITERATURE AND RE- PORT OF TWO ADDITIONAL CASES *

By EUGENE L. ARMSTRONG, M D , F A C P , W L ADAMS, JR , M D , L J
TRAGERMAN, M D , and E W TOWNSEND, M D ,
Los Angeles, California

INTRODUCTION

In 1833 Pegot¹ observed a patient who presented the phenomena of dilated veins in the abdominal wall, with a caput Medusae and a loud venous murmur at the umbilicus. At necropsy a widely patent umbilical vein, a small but apparently grossly normal liver and a large spleen were found. The details of this case were published and elaborated by Cruveilhier². He believed that the patient was probably suffering from a congenital defect of the umbilical circulation, with atrophy of the liver, probably secondary to this defect. In 1908, Baumgarten³ reported the case of a 16 year old boy who had distended abdominal veins, ascites, splenomegaly, anemia, and leukopenia. Death followed a gastric hemorrhage, and necropsy revealed a widely patent umbilical vein, splenomegaly "not of the Banti type," and an atrophic liver with subcapsular increase in fibrous tissue. Microscopically the hepatic lobules were small but otherwise normal, with only scattered increase in interlobular connective tissue. Baumgarten emphasized the absence of a well-developed cirrhosis and the patency of the umbilical vein itself, as essential features of the disease. He believed that the disease was based on hypoplasia of the liver, probably congenital in origin, associated with patency of the umbilical vein and venous stasis in the spleen.

A number of similar cases, usually designated "Baumgarten's cirrhosis," have been reported in the foreign literature since 1908. In 1922 Hanganutz⁴ introduced the name "Cruveilhier-Baumgarten cirrhosis" which has been generally used by authors of subsequent case reports and theses⁵ on the subject.

Our interest in this subject was aroused by the clinical study of two patients, one also at necropsy, showing many features of the disease as originally described by Cruveilhier and Baumgarten. In both instances, ante-mortem diagnosis of Cruveilhier-Baumgarten syndrome was made by members of the hospital attending staff.

No direct reference by name to the Cruveilhier-Baumgarten syndrome appears in the English literature, although cases described by Thayer,⁶

* Received for publication August 14, 1940

From the Department of Medicine of the College of Medical Evangelists, the Department of Pathology of the University of Southern California School of Medicine, and the Laboratories of the Los Angeles County Hospital

Henry,⁷ Wollaeger and Keith,⁸ include features suggestive of this disorder. Moschkowitz,⁹ and Johnson,¹⁰ refer indirectly to the disease in papers on Banti's disease and allied disorders. Because of the lack of accurate description of this syndrome in the English literature, we have reviewed the cases reported under the name Cruveilhier-Baumgarten disease, as well as the cases otherwise designated by various authors, in order to establish the existence and nature of the disease, if possible. The original case reports, as well as the several theses that have appeared on the subject in the foreign literature,^{5,9} were consulted whenever available. Analysis of the various cases thus reported shows that considerable deviation exists from the clinicopathologic picture first described by Cruveilhier and Baumgarten. We have, therefore, listed all pertinent etiologic, clinical and pathological data available in the various case reports, and shall attempt to summarize and analyze them in the light of the original descriptions. We were able to find 52 previously reported cases which are summarized in table 1. To these we have added our two cases, and an additional case found in the autopsy protocols of the Los Angeles County Hospital, which is included in table 1 as case 53.

CASE REPORTS

Case 1 (number 54 in table 1). L. A., a Spanish female, aged 41, housewife, was first admitted to the Los Angeles County Hospital May 22, 1937, complaining of sudden onset of nausea, accompanied by vomiting of blood in large amounts some seven hours previously. In March 1936, the patient noticed distended veins over the lower portion of the sternum and upper abdomen. These produced no symptoms and she did not consider them significant. Her entry to the hospital was precipitated by a sudden severe pain across the epigastrium, accompanied by weakness and vomiting of approximately two and one-half quarts of bright red blood and large clots.

Past History. At the age of 10, the patient was operated on for the repair of an "umbilical hernia." Hospital records are not available for more complete information, but she recalls no local vascular disturbance of the umbilicus at that time. She had drunk one glass of wine with her meals for years. She had a positive blood Wassermann reaction in 1928 which became negative following a "course of treatment." Inventory by systems was essentially normal.

Physical examination revealed a well-developed and well-nourished female, in acute distress, vomiting at intervals considerable quantities of bright red blood and clots. The blood pressure was 135 mm Hg systolic and 90 mm diastolic. There was an old healed midline incision in the lower abdomen. Several large, dilated and tortuous veins were noticed between the umbilicus and the sternum, disappearing from view near the xiphoid process (figure 1). On auscultation, a loud, roaring, continuous murmur was heard at the xiphoid process and just superior and to the right of the umbilicus. Thrills were palpated in these areas. The spleen was readily palpable, extending to the level of the umbilicus. The liver was not palpable and no ascites was demonstrable. Physical examination was otherwise negative.

Laboratory Examination. The urine was essentially normal. The hemoglobin was 75 per cent, erythrocytes 3,690,000, and leukocytes 6,250 with 81 per cent neutrophils. The platelets were normal. The reticulocytes were 137 per cent. Blood Wassermann and Kahn tests were positive. The fragility test showed initial hemolysis at 0.42 and complete at 0.49. The icterus index was 6.6 units. Plasma

fibrinogen was 229 mg per 100 cc of blood plasma. The urea nitrogen was 10 mg per cent. Roentgen-ray of the chest on May 26, 1937, was essentially normal.

Clinical Diagnosis Cirrhosis of liver, portal hypertension and splenomegaly, bleeding esophageal varices and syphilis.



FIG 1 Infra-red photograph of Case 1. Arrows indicate areas of loudest murmurs.

Course In the hospital, the patient continued to have hematemesis from time to time, which decreased in amount and gradual improvement was noticed. On June 3, 1937, she was presented to the floor conference of the hospital medical department and the diagnosis of Cruveilhier-Baumgarten disease was suggested by Dr. V. R. Mason.

TABLE I

No	Author— Date	Sex	Age	Etiol *	Symptoms	Physical findings	Laboratory findings	Diagnosis
1	Pegot- Cruveilhier 1833-35	M	48	A T C	Abdominal pain fol- lowing trauma in 1813, prominent veins in 1814 which increased in size during next 13 years Gastric symp- toms leading to death in 1833	Dilated veins with a caput me- dusae Slight murmur heard with stethoscope at umbilicus		"Scurrhus" at pylorus
2	Bamberger 1851					Thrill and murmur at sternum and umbilicus		Cirrhosis
3	Bouvillaud- LeMaire 1859	M	43	—		Murmur at sternum		Cirrhosis
4	Trousseau- Sappey 1859	F	50	—		Thrill and murmur heard over abdominal veins		Cirrhosis
5	Davies 1863					Epigastric murmur		Hepatic cirrhosis
6	Giacomini 1873	F	22	—		Enlarged spleen No murmur or thrill		Cirrhosis.
7	Picchini 1890	M	16	—		Thrill and epigastric bruit		Cirrhosis
8	Bordoni 1890	—	41	M		Tremor and epigastric murmur 2 to 3 cm above umbilicus En- larged liver and spleen Caput medusae		Cirrhosis
9	Audry 1892	—	50	—		Continuous murmur over xiphoid and umbilicus Enlargement of liver and jaundice		Pneumonia
10	Von Jaksch 1893	—	—	—		Epigastric venous sound Liver and spleen enormous		Cirrhosis
11	Von Jaksch 1893	—	—	—		Left epigastric venous sound Liver and spleen enormous		Cirrhosis
12	Rolleston	M	43	—		Epigastric murmur and devil's sound in neck		Cirrhosis
13	Piazza- Martini 1894	—	—	—		Slight low murmur on hepatic area especially in right arm pit differing from hepatic murmur Epigastric venous sound in course of develop- ment of disease		Cirrhosis Syphilis (hereditary)
14	Taylor 1895	M	20	S	Swelling of abdomen with vomiting from age of 6 Hemar- temesis	Epigastric venous sound in course of development of disease		
15	Gambartini 1903	M	45	—		Venous hum with diastolic strengthening located at the base of the xiphoid appendix, disap- pearing on constriction Liver small, spleen enlarged, old pleu- risy		
16	Catti 1903	—	—	—		Thrill Loud murmur character- istic venous murmur on tegmen- tous epigastric vein and to the left of it		Cirrhosis with epigas- tric varicose veins

* A, alcohol S, syphilis M, malaria C, congenital T, trauma

TABLE I (Continued)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No
	Gross Small but normal Micro Not described	Persistence and dilatation of umbilical vein	Gross Large and indurated, three times normal weight Micro Not described	Benign obstructing lesion of pylorus	1
		Patent umbilical or paraumbilical vein			2
	Gross 18 x 14 cm in size Micro Cirrhosis	Portal vein normal Umbilical vein not examined	Gross 24 x 15 cm only description Micro Not described		3
		Paraumbilical vein discovered by Sappey			4
				Not dead at time of report	5
	Gross Cirrhotic liver Micro Not described	Dilatation of paraumbilical vein			6
	Gross Small liver Micro Not described	Patent umbilical vein	Gross Large spleen only comment Micro Not described		7
				Not dead at time of report	8
				Not dead at time of report	9
		Anomaly where coronary vein empties from ventricle (text obscure) No doubt that murmur originates from coronary vein of stomach			10
		Splenic vein as large as little finger. Dilatation at all tributaries of portal vein, as well as those of epiploic and ligamentum teres. Slightly different from other venous sounds (murmur originated in splenic vein)			11
		Round ligament contains a closely crowded vein as thick as the little finger (paraumbilical)			12
				Not dead at time of report	13
	Gross Liver cirrhotic Micro Not described		Gross Spleen enlarged Micro Not described	No other anatomical investigation	14
				No autopsy	15
		Ligamentum teres very large and thickened Subperitoneal veins Passage of blood from small vessels into veins was noted			16

TABLE I (Continued)

No	Author— Date	Sex	Age	Etiol	Symptoms	Physical findings	Laboratory findings	Diagnosis
17	Catti 1903	M	51	—		Marked venous sound at junction of xiphoid-sternum, increased by inhalation No thrill Spleen enlarged Ascites present Abdominal veins absent		Atrophy cirrhosis
18	Scheele 1904	M	45	—		Thrills in umbilical region and devil's sound increased by inhalation Jaundice, dropsy and hepatomegaly		
19	Baumgarten 1908	M	16	C	Swelling of abdomen with dilated abdominal veins, generalized weakness	Ascites, splenomegaly, anemia and dilated abdominal veins The absence of murmur and thrill is described	R B C 33 M W B C 2,600	Banti's disease
20	Thayer 1911	M	49	A	Hematemesis for two years with right-sided abdominal pain	Blanched Pulse 100 regular and soft Blowing precordial murmur Liver palpable, spleen enlarged, abdomen full, veins distended Loud continuous venous hum at xiphoid Fever to 101°	Hb 30% R B C 34 M Hb 56% W B C 4,000 Hb 75% Urine negative	Portal cirrhosis
21	Masuda 1911	F	48	M prob	Anemia and nephritis mentioned in history		R B C 18 M W B C 1,150	Banti's disease Chronic nephritis
22	Oettinger 1911	M	30	—	Vomiting of blood and slight jaundice Melena	No murmur or thrill Spleen enlarged Liver normal	Urobilinuria	Banti's disease
23	Henry 1912	M	70	A	Fatigue dyspnea and swelling of ankles for 4 mos	No thrills but continuous loud murmurs over ensiform Prominent anastomosing veins over abdomen No ascites Liver not palpable No edema		Cirrhosis of liver
24	Benque 1912	M	18	A?	Swelling of abdomen and lower extremities of 3 months' duration	Ascites large spleen, small and painless liver	R B C 40 M Hb 80% W B C 3,000 Wassermann negative	Banti's disease
25	Eppinger and Rinzl 1920	M	15	—	Epistaxis melena vomiting with hematemesis Tuberculous peritonitis in childhood	Liver hard and irregular 4 fingers below the costal margin Tremor over ectased veins between umbilicus and xiphoid process Thrill present Splenomegaly, anemia and peripheral edema		Baumgarten's disease

TABLE I (Continued)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No
				Not dead at time of report	17
				Not dead at time of report	18
Hematemesis and thrombosis of epigastric veins following Talmi operation	Gross Liver greatly atrophied, 18 x 13 x 7 cm, particularly left lobe (length 7 cm), capsule somewhat thickened, external surface irregularly coarse and knobby. At beginning of ligamentum falciform are "tied off" knots of liver tissue. Cut surface shows increased connective tissue in region below capsule and some general coarseness. Micro Considerable interlobular fibrosis in outer portions of liver coming down from capsule. Elsewhere periportal tissue not thickened and scarcely any connective tissue formation to be seen between acini. Acini small but otherwise normal.	Large patent umbilical vein communicating with epigastrics and veni porta filled with thrombus. Deep epigastric veins also thrombosed.	Gross 26 x 13 cm. Greatly enlarged, with infarctions present. Micro Not described.	Bone marrow gray-red in color.	19
Coma and convulsions				No autopsy. Died in coma.	20
	Gross Atrophic and slightly cirrhotic. Micro Not described.	Patent and dilated umbilical vein with a caput medusae.	Gross Enlarged spleen with phlebosclerosis of splenic vein. Micro Not described.	Circumscribed endophlebitis of vena cava and hepatic veins. Kidney showed chronic nephritis and heart was hypertrophied.	21
Died during splenectomy	Gross Liver cirrhotic. Micro Not described.	Dilated epigastric veins and dilated "vein of round ligament." Dilated splenic vein.	Gross Enlarged. Micro Fibroaden.		22
Pulmonary edema	Gross Small and granular liver. Micro Not described.	Venous sinuses adhering to anterior edge of liver just below xiphoid cartilages. Xiphoid perforated by veins connecting reticulo-xiphoid sinus.	Gross Lowered by adhesions. Micro Not described.	Venous sounds originated in sinus and transmitted through blood vessels perforating ensiform.	23
	Gross Weight 820 gm. Left lobe transformed into small connective tissue formation. Right lobe coarsely granular. Micro Not described.	Patent umbilical vein communicating with internal iliac vein.	Gross 1350 gm. Hypertrophied but hypertrophy due to stasis and not to fibroaden. Micro Enlarged sinuses very fibrous. Cell rich tissue seen in depths. Not Banti's.		24
Hematemesis	Gross Small and atrophic liver. Micro Not described.	Umbilical and epigastric veins anastomose with marked dilatation.	Gross Splenomegaly. Micro Not described.	Pathogeny described as compression by tuberculous peritonitis or by cirrhosis.	25

TABLE I (Continued)

No	Author— Date	Sex	Age	Etiol	Symptoms	Physical findings	Laboratory findings	Diagnosis
26	Eppinger and Ranzi 1920	F	23	—	Distention of abdomen with edema Increased thirst Polyuria Loss of weight	Murmur and tremor synchronous with cardiac rhythm between umbilicus and xiphoid process Liver and spleen enlarged Ascites and edema present		
27	Florand 1922	M	28	S A		Murmur and tremor palpated over two varicose lumps, one at the xiphoid and the other at the umbilicus Edema, ascites and splenomegaly		
28	Huber 1922	M	45	S A		Continuous systolic murmur and thrill from lower edge of venous tumor above and to the right of the umbilicus Liver and spleen hypertrophied		Cruveilhier Baumgar- ten's cirrho- sis
29	Hanganutz 1922	F	53	S A	Epigastric pain fol- lowed by distention and swelling	Dilated vein between xiphoid and umbilicus 11 cm long and size of little finger Definite thrill at xiphoid Atrophied right lobe of liver but large left lobe which was irregular and tender Spleen hypertrophied	Hb 80% Urine Pus and hyaline casts Wassermann positive	Baum- garten's cirrhosis
30	Akil Mouk- tar 1924	F	50	—		Venous murmur with intense thrill at base of xiphoid Ascites and edema Prominent abdominal veins		
31	Popper 1924	M	43	M A	Lumbar pain and cough Red and ul- cerated skin Erup- tion on legs Dilated abdominal veins of un- known duration	Dilated and tortuous thoraco-abdominal veins chiefly from xiphoid to umbilicus Caput medusae around umbilicus Blood flow away from umbilicus Tremor and "mill-like" murmur in sub-xiphoid region Large spleen	Urine negative Hb 70% R B C 3 69 M W B C 5 400 Polys 76% Wassermann negative	Cruveilhier Baum- garten's syndrome
32	Bastai 1925	F	—	—				
33	Bastai 1925	F	—	—				
34	Vissicano 1927	—	—	M		Murmur and thrill between ensi- form and umbilicus Small liver and hypertrophied spleen		
35	Charbrol and Bernard 1929	—	—	—		Continuous murmur over dilated vein extending from saphenous vein to umbilicus		
36	Gallardo and Gravito and Puig 1928	—	—	—		Hollow spinning wheel sound at lower third of sternum Hepatic cirrhosis		

TABL I (Continued)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No
Generalized peritonitis	Gross Small and nodular cirrhotic liver Micro Not described	Veins as large as the little finger were found in the round ligament connecting between the portal and epigastric veins	Gross 1000 gm Capsule thickened Perisplenitis Micro Pulp shrunken Stroma not particularly increased		26
	Gross Cirrhotic, 1090 gm 17 x 13 cm Atrophy diffuse but predominantly right-sided Micro Periportal fibrosis with atrophy of liver cells and disorganized architecture	Round ligament permeable from umbilicus to hilum of liver	Gross 2020 gm 30 x 16 cm with dense perisplenitis Micro Increased fibrous tissue	Kidney revealed an adherent capsule and microscopically showed small glomeruli with swollen capsules, degeneration of tubular epithelium and some increased fibrosis	27
				Not dead at time of report	28
				Not dead at time of report	29
	Gross 1150 gm with atrophy of right lobe and hypertrophy of left Micro Not described	Right branch of portal vein smaller than left. Adhesive phlebitis at forking of two branches			30
				Not dead at time of report	31
	Gross Surface of liver covered with reddish nodules varying in size Micro Portal vessels surrounded with connective tissue and in great measure occluded by recent thrombi. Biliary ducts filled with thick transparent bile	Great dilatation of portal vein with large recent thrombus in its principal branch to the hilum. No large supra-hepatic veins found. On right was a small sac which communicated with the lumen of the vena cava. No opening for the left branch was found. Umbilical vein was patent	Gross Dilated splenic vein. Thickened capsule Micro Not described		32
	Gross Enlarged and hard Micro Not described	Branches and trunk of the portal vein appeared permeable. The round ligament was traversed by a central vein, the umbilical which communicated with the left branch of the portal and anastomosed with the epigastrics. The openings of the supra-hepatic veins into the vena cava were like small whitish tufts resembling thrombi. The branch of the left lobe less restricted than the right	Gross Normal Micro Not described		33
		Dilated paraumbilical vein. Two other veins near by			34
				Not dead at time of report	35
				Partial autopsy was negative	36

TABLE I (Continued)

No	Author— Date	Sex	Age	Etiol	Symptoms	Physical findings	Laboratory findings	Diagnosis
37	Kaufman 1929	M	30	—		Thrill and murmur over flexuous vein leading from umbilicus to xiphoid appendix Large liver and spleen Edema of extremities but no ascites		
38	Pagniezet and Rivoire 1929	M	34	M	Severe pain in right hypochondrium Lassitude and asthenia	Enlarged abdomen with no ascites Liver normal Spleen enlarged No dilated veins Loud murmur at xiphoid appendix Thrill present		Cruveilhier Baum- garten's cirrhosis
39	Lupu and Gingold 1929	—	26	—		Continuous murmur and grinding sound stronger in systole noticed at ensiform umbilical area and another between the umbilicus and pubis Dilated veins in umbilical xiphoid region Liver and spleen large	R B C 18 M W B C 1,600	
40	Brittana Visineano and Solomon 1929	M	43	M	Lumbar, precordial pain and dry cough Varicose veins of abdomen from birth Loss of weight Fever	Enormous varicose veins between xiphoid and umbilicus Murmur and thrill Spleen palpated Flow of blood from central region toward brain Slight jaundice Liver small Ascites and edema present	Hb 80% R B C 38 M W B C 5400 Wassermann negative	Cruveilhier Baum- garten's disease Aortic stenosis with insufficiency
41	Fiessinger and Michaux 1930	F	51	A	Digestive disturbance and jaundice at age of 18	Abdominal distention No ascites Many veins especially in umbilical region with thrill and murmur to left of umbilicus Liver and spleen large	Wassermann negative	Cruveilhier Baum- garten's disease
42	Fiessinger and Michaux 1930	M	59	S M A	Hematemesis	Abdomen distended with collateral circulation marked around umbilicus Liver enlarged and firm Spleen not palpated Continuous murmur above umbilicus No thrill Recurrent ascites	R B C 14 M Urine bile and albumin Rose Bengal 725	Cirrhosis
43	Quasch 1930	M	30	—	Epistaxis and vomiting	Thrill and murmur over venous tumor at umbilicus for 10 years Splenomegaly		
44	Figuerido 1930	M	66	T	Severe blow in supra-umbilical region Abdominal pain and icterus Progressive loss of weight and distention of abdomen	Unilateral network of veins above umbilicus with murmur and thrill Splenomegaly and icterus	Blood sug —63, Wassermann negative W B C 6500	Biliary cirrhosis
45	Fontanel and R Puig 1931	F	35	—	Digestive disturbances Oct. 1929, jaundice and oliguria Dec 1929, distention of abdomen Jan 1930, murmur at xiphoid March 1930	Jaundice Ascites Collateral circulation not well developed Liver small, spleen large		Cruveilhier Baum- garten's disease
46	Puig and Gilibern 1933	M	40	A	Jaundice for 20 years with attacks lasting 2 weeks Hematemesis 9 years	Venous murmur along course of vein in midline below xiphoid Thrill present, large tender liver and enlarged spleen	Wassermann negative Fragility normal W B C 3000 Polys 68%	Cruveilhier Baum- garten's disease

TABLE I (Continued)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No
			-	Not dead at time of report	37
				Not dead at time of report	38
				Not dead at time of report	39
Cachexia Hyperthermia	Gross 1100 gm Small and furrowed Right lobe atrophied Caudate lobe hypertrophied Appearance and color normal, lobular markings obscured Micro Smallness of lobules and endophlebites Increased periportal fibrosis Central veins showed slight sclerosis and intralobular capillaries were dilated Diag Slight sclerosis without cirrhosis	Practically entire absence of right branch of portal vein Left branch large opening into "rest" canal which opened into paraumbilical vein This continued to the abdominal wall running superiorly and then became superficial at the xiphoid in a venous chamber and anastomosed with the epigastric, internal mammary and subcutaneous thoracic veins	Gross 1200 gm Patchy perisplenitis On cut section follicles were not apparent Micro Rich in cellular elements Malpighian corpuscles normal but splenic trabeculae hypertrophied Diag Stasis and chronic splenitis	Heart showed aortic and mitral valvulitis No varices in esophagus or rectum Lungs revealed a chronic pleuritis with apical tuberculosis	40
Hepatic insufficiency				No autopsy Died from hepatic insufficiency	41
Coma	Gross 1450 gm Annular cirrhosis Micro Not described	Umbilical vein widely patent	Gross 140 gm Micro Corpuscles diminished in number and size	Kidneys were normal	42
				Not dead at time of report	43
Fetid bronchitis	Gross 1300 gm Irregularly granular Micro Ring shaped cirrhosis intense especially in right lobe No new formed bile ducts Portal vessels dilated few leukocytes Marked granular swelling of liver cells	Umbilical vein patent and equal in size to the portal vein in its two branches	Gross Enlarged three times Micro Not described	Jaundice Chronic pericarditis Anatomical diagnosis of hepatic cirrhosis with patent umbilical vein	44
Hepatic insufficiency with coma				No autopsy Died of hepatic insufficiency	45
	Gross 1000 gm Studded appearance typical of cirrhosis Micro Perilobular cirrhosis and inflammatory islands	Umbilical vein permeable and dilated up to 2 cm from the umbilicus where it anastomosed with paraumbilical veins	Gross 600 gm Micro Not described		46

TABLE I (Continued)

No	Author— Date	Sex	Age	Etiol	Symptoms	Physical findings	Laboratory findings	Diagnosis
47	Spinelli and Pana 1934	M	16	—	Mild attacks of icterus	Ascites, distended abdominal veins Spleen not enlarged		
48	Forns Barcelo 1935	M	25	A	At age 18 a doctor noticed splenomegaly and dilated veins at epigastrium Symp- toms began at age 21 with pallor, asthenia and later hematemesis	Souffle and continuous thrill over xiphoid, varicose mass of veins in paraumbilical region Liver not palpable Marked splenomegaly Pallor and sub-icterus At sur- gery, enormous spleen without adhesions with vascular hilus and abdominal wall	Urobilinuria Hb 70% R B C 3 0 M W B C 3,000 Polys 72% Platelets, 100,000 Wassermann negative	Cruveilhier Baum- garten's disease
49	Rossi and Anbrien 1935	F	50	—	Pains in right hypo- chondrium and epi- gastrium Scanty urine, dark in color at times	Distended veins over thorax and abdomen Liver irregular and hard, just below costal margin Spleen enlarged No fluid	R B C 4 2 M W B C 7 400 Polys 57% Wassermann negative Urine negative	Cruveilhier Baum- garten's syndrome
50	Lutembacher 1936	M	53	—	At age of 41 had a large liver with distended abdominal veins and diarrhea 1935 developed ascites and edema of scrotum	Distended abdomen with dilated abdominal veins Continuous murmur below xiphoid of spin- ning wheel type with a perceptible thrill Another mass of veins 10 cm from umbilicus with murmur Liver small Spleen large and ascites present	Urine negative Wassermann negative	
51	Guez 1936	M	32	—	Large dilated veins over abdomen for 9 years	No murmur Large liver, firm and smooth No spleen or ascites	Urine Albumin	Cruveilhier Baum- garten's disease
52	Wollaeger and Keith 1938	M	38	—	Fever of 8 months' duration Hema- temesis in 1933 fol- lowed by jaundice and ascites Omentopexy in 1933 and cirrhosis of the liver were noted at surgery	In the region of the xiphoid there was a continuous harsh roaring murmur and palpable thrill Di- lated veins with a small liver and splenomegaly High pulse pres- sure, capillary pulse and over- active heart	Urine negative Kahn negative Hb 11 6 gm R B C 3 3 M W B C 3,000 Urea 20 Total proteins 6 8 Albumin 3 4 Globulin 3 4	1 Banti's syndrome with cir- rhosis of liver 2 Possible arterio- venous fistula
53	Dodson 1930 ¹	F	2	—	Jaundice for several weeks at birth, ab- dominal distention for several weeks before death	Abdomen distended from ascites (1000 c c withdrawn), no murmurs or dilated abdominal veins de- scribed	R B C 3 9 M W B C 22 000 Cholesterol 152	Cirrhosis of liver
54	Authors first case	F	41	A?	Distended abdominal veins since 1936, hematemesis before entry to hospital	Distended thoraco-abdominal veins, murmur and thrill at xi- phoid and umbilical areas, pal- pable splenomegaly, liver not pal- pable	R B C 3 6 M W B C 6,200 Blood Wass and Kahn posi- tive Icteric ind 6 Urea N 10	Cruveilhier Baum- garten's syndrome
55	Authors' second case	M	25	—	Abdominal swelling, 2 months	Caput medusae with continuous thrill and murmur at umbilical area, ascites	R B C 4 2 M W B C 5,200 Icteric ind 5	Cruveilhier Baum- garten's disease

¹ Unpublished necropsy observation

TABLE I (Continued)

Cause of death	Liver	Portal system	Spleen	Miscellaneous	No
Died after omentopexy	Gross Chronic passive congestion of the liver Micro Not described	Patent umbilical vein		Old thrombosis of trunk of vena cava, suprahepatic, renal, spermatic and iliac veins Abdominal and thoracic veins dilated	47
Hematemesis	Gross Small atrophic and granular, especially the left lobe Micro Not described		Gross Not described Micro Thickened trabeculae with fibroaden	Esophagus and stomach revealed no site for the source of the hemorrhage	48
				Not dead at time of report	49
Hematemesis	Gross Atrophic Laennec's cirrhosis Micro Showed cirrhosis without degeneration of uninvolved liver cells	Umbilical vein not patent. Para-umbilicals large and dilated (1 cm) flowing into the left portal vein	Gross Spleen large Micro Not described	Kidneys heart and aorta were normal	50
				Not dead at time of report	51
				Not dead at time of report	52
Pneumococcal septicemia	Gross 460 grams 15 x 10 x 9 cm. Broad scars and scattered nodules up to 2 cm in diameter Micro Portal cirrhosis	Umbilical vein widely patent	Gross 110 grams, firm Micro Severe chronic passive hyperemia		53
Still alive					54
Gastric hemorrhage	Gross 1300 grams, smooth, firm, fine periportal scarring with occasional tiny nodules Micro Atrophy and periportal fibrosis	Umbilical vein widely patent	Gross 900 grams, firm with prominent trabeculae and obscured follicles Micro Increased connective tissue elements, dilated sinusoids		55

The patient left the hospital August 18, 1937. She was not seen again until March 13, 1939, when she returned because of massive hematemesis of 24 hours' duration. With this admission she was acutely ill, quite pale, with blood pressure 115 mm Hg systolic and 70 mm diastolic. The spleen was enlarged and the abdominal murmurs and thrills were present as before. The blood count revealed hemoglobin of 48 per cent (Sahli), white blood cells 8,500 with 86 per cent polymorphonuclears. Blood transfusion was given, followed by slow improvement and cessation of bleeding. Additional laboratory findings before discharge were serum albumin 2.8 gm, cholesterol 185 mg and cholesterol esters 134 mg per 100 cc of blood.

With this last admission, splenectomy was tentatively suggested to the patient, but refused. She was then referred to the Out-Patient Clinic for observation and continuance of antiluetic therapy.

Case 2 J S, a white American poultryman, aged 25 years, was admitted to the Los Angeles County Hospital January 28, 1938, complaining chiefly of swelling of his abdomen, of about two months' duration. He stated that he had been in good health until three years before, when he developed "kidney trouble," as evidenced by nocturia, low backache, and high blood pressure. At about this time, he noticed incidentally some swelling of the veins of the right side of the abdomen. Two months before entry, edema of the ankles, together with increasing ascites developed, necessitating paracentesis (7 liters), and he had two episodes of vomiting of small amounts of coffee-grounds material. He had also noticed failing vision for two weeks prior to entry.

Past history revealed no definite infections. He stated that he had consumed an average of a pint of whisky per month since the age of 14 years.

Physical examination revealed a somewhat emaciated white male in no acute distress. Temperature, pulse, and respirations were normal. The pupils reacted poorly to light and convergence. Ophthalmoscopic examination by Dr. Warren Wilson revealed pigmentary retinitis and papillitis. The lungs were clear. The heart was enlarged to the left and a soft, systolic murmur was heard at the apex. The blood pressure was 160 mm Hg systolic and 90 mm diastolic. The abdomen was markedly distended and numerous dilated and tortuous veins radiated from a caput medusae (figure 2). A soft, continuous murmur was heard just above and to the right of the umbilicus, where a thrill was felt. A definite fluid wave was present and the spleen was enlarged. The liver was not palpable. No other abnormalities were noted.

Laboratory The urine was essentially normal except for moderately impaired concentration. Blood count revealed hemoglobin of 40 per cent (Sahli), erythrocytes 4,200,000, leukocytes 5,200 with 90 per cent polymorphonuclears. The Wassermann and Kahn reactions were negative. The non-protein nitrogen was 75 mg per cent, creatinine 3.3 mg per cent, icterus index 5 units, albumin 2.3 grams per cent, globulin 2.4 grams per cent. The electrocardiogram showed sinus tachycardia.

Course On February 5, 1938, the patient was peritoneoscoped by Dr. John C. Ruddock, and 4,500 cc of clear, colorless fluid were removed. Atrophy, apparent fibrosis, and capsular thickening of the liver were noted externally, making biopsy impossible. The spleen was enlarged. It was also noted that there was a large, tortuous, dilated vein occupying the site of the ligamentum teres.

The patient's condition continued to grow worse, with several lapses of consciousness and convulsions during the week prior to his death. He died April 12, 1938, following a massive gastric hemorrhage. The clinical diagnosis was Cruveilhier-Baumgarten syndrome with gastric hemorrhage, chronic glomerulo-nephritis, and retinitis pigmentosa.

Necropsy* was performed 20 hours after death on an already embalmed body by one of us (I. I T) The following is a summary of the gross and microscopic findings



FIG 2 Infra-red photograph of Case 2 showing caput medusae

External Examination Body is that of a fairly well developed but poorly nourished young white male Abdominal distention and prominence of tortuous superficial veins over the abdomen are still evident, as well as the scars of paracentesis Slight pitting

* We are greatly indebted to Dr C V Atteberry for his interest in this case, and his aid in obtaining permission for autopsy

edema of the lower extremities is present. Skull and central nervous system are not examined, and the neck organs appear normal in situ. The only abnormalities noted in the thorax are moderate hyperemia of the lungs with some bloody fluid in the bronchi and evident hypertrophy of the left ventricle which averaged 2 cm in thickness. The weight of the heart is estimated to be 400 grams. The principal findings of interest were in the abdominal wall, digestive system, liver, and portal system. The abnormal veins found in the abdominal wall will be described largely in connection with the liver.

The peritoneal cavity contains about six liters of clear light amber fluid. All surfaces are smooth and glistening. The esophagus is dilated to about three times normal caliber throughout, particularly near the cardia. Some dilated veins are present along the outer wall of the esophagus, but no varices within the wall are noted. The cardiac sphincter appears normal. The stomach is dilated to at least twice normal capacity by a mixture of almost black liquid blood plus recent clots. The wall of the stomach is thin, the mucosa is smooth but marked by a number of pinhead hemorrhagic spots, none grossly certain to be erosions. The pylorus is normal. The small intestine is about average length and extreme edema is present throughout. On the mucosal surfaces of the jejunum, zones of edema involving the folds of mucosa produce the appearance of multiple polyps. In addition, in the terminal ileum, there are some areas of superficial erosion of the mucosa. Mesenteric veins surrounding these erosions are markedly dilated. The appendix is normal. The large bowel is moderately edematous, and in some areas the same polypoid edema noted in the mucosal folds of the small bowel is present. The pancreas is of average size, cut surface is firmer than normal, and the lobular markings are somewhat accentuated.

In the dissection of the abdominal wall, plexuses of veins both above and below the umbilicus are noted in the subcutaneous tissues, as well as in the recti muscles and sheaths. These veins lead toward the costal margin, the region of the xiphoid, and the femoral area. The largest are epigastric veins leading to the femoral veins. These veins, particularly the epigastric, communicate directly with an aneurysmal venous dilation, 6 cm in diameter, situated just beneath the umbilicus (figure 3). From here a large vein replaces the ligamentum teres and runs in the edge of the falciform ligament to the liver. This is interpreted as a persistent and dilated patent umbilical vein. A somewhat smaller vein leads from the umbilical region toward a plexus of veins about the ensiform cartilage. The umbilical vein opens without difficulty into the left branch of the portal vein. As it traverses its fossa in the liver in a groove in the quadrate lobe, small branches can be seen going directly to the liver. Remnants of the ductus venosus lie in a ligamentous cord in the usual situation near the caudate lobe. This duct is only partially patent and when injected under pressure with colored liquid solution, its stenosed mouth in the inferior vena cava is indicated by staining of the wall without actual escape of the solution into the inferior vena cava.

The liver weighs 1300 grams and is smaller than normal, particularly in the vertical diameter. The average diameters are transversely, 15 and 8 cm for the right and left lobes respectively, vertically, 8 cm for the right lobe, and antero-posteriorly, 15 cm. The quadrate lobe averages 6 cm in transverse diameter, the caudate lobe, which is smaller than normal, measures 3 by 1.5 cm. The external surface of the liver is smooth, free of the diaphragm, and scattered telangiectatic venules are visible beneath the slightly thickened capsule. The liver cuts with increased resistance, exposing purple-gray to light brown surfaces. On closer inspection there appears to be accentuation of lobular markings by increase of fine fibrous periportal tissue without distinct nodular formation (figure 4). The gall-bladder is distended by thin bile, otherwise it is normal, as is the biliary tract.

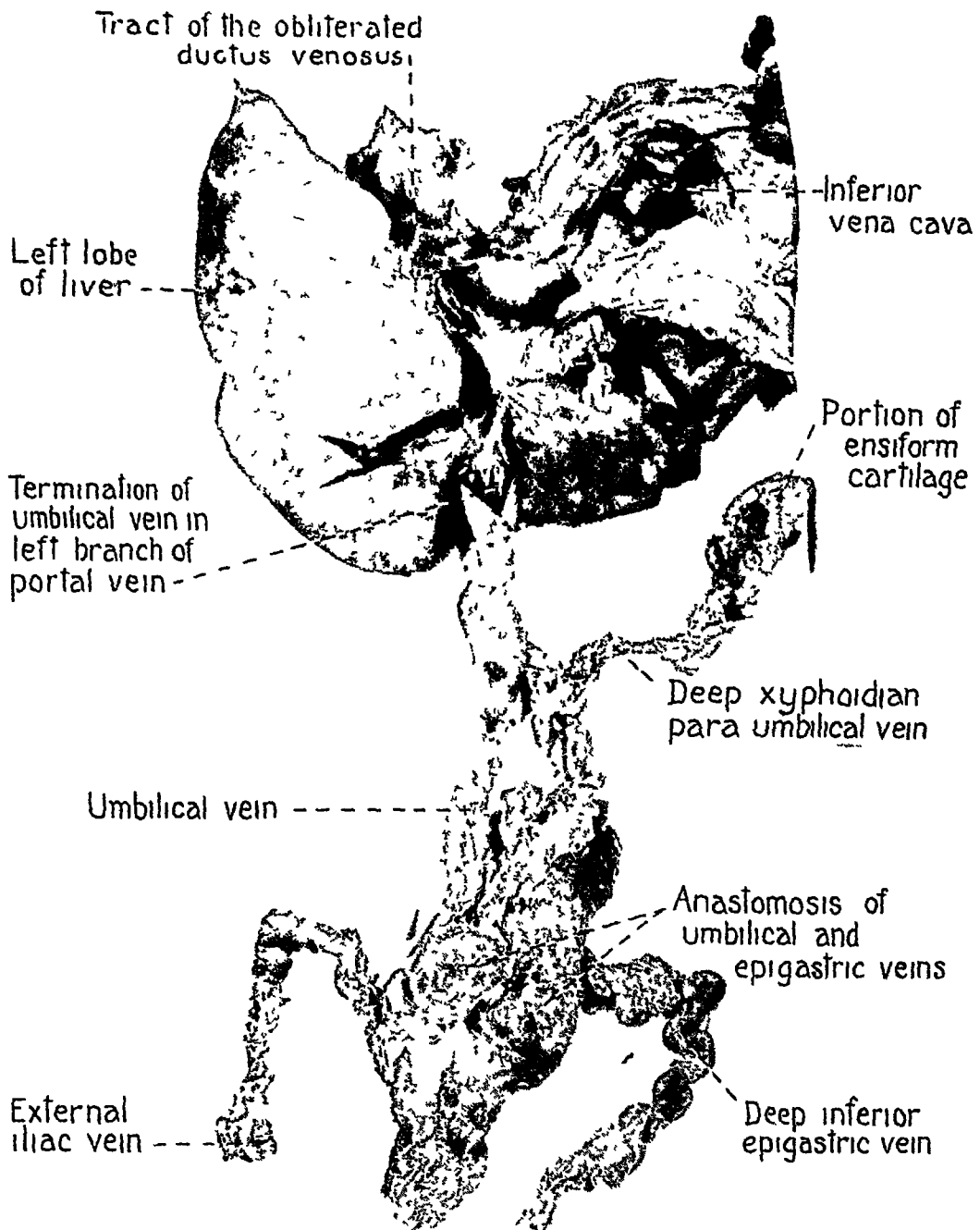


FIG 3 Showing connections of patent umbilical vein with thoraco-abdominal veins and portal vein

The total length of the inferior vena cava is 25 cm with an average circumference of 3.5 cm. The mouths of the hepatic veins appear normal. In the superior group there are two veins, one from the right and left lobes respectively. In the inferior group there are five veins with slit-like openings. The branches of the hepatic veins appear normal as far as they can be traced. The portal vein is 7 cm

in length, its average circumference is 3 cm (normal 1.5 cm), and its right and left main branches are 0.5 and 3 cm respectively, each having an average circumference of 1.5 cm. The secondary branches are traced with some difficulty, the supporting connective tissue being noticeably thickened. The intima of the portal vein is smooth and occasionally slightly thickened. The umbilical vein is 23.5 cm in length with an average diameter of 2 cm, and joins the left branch of the portal almost 3 cm from the origin of the latter. All major tributaries of the portal vein are dilated to at least twice normal diameter. Occasional slight thickening without gross plaque formation is present in the intima of the splenic and superior mesenteric veins. These

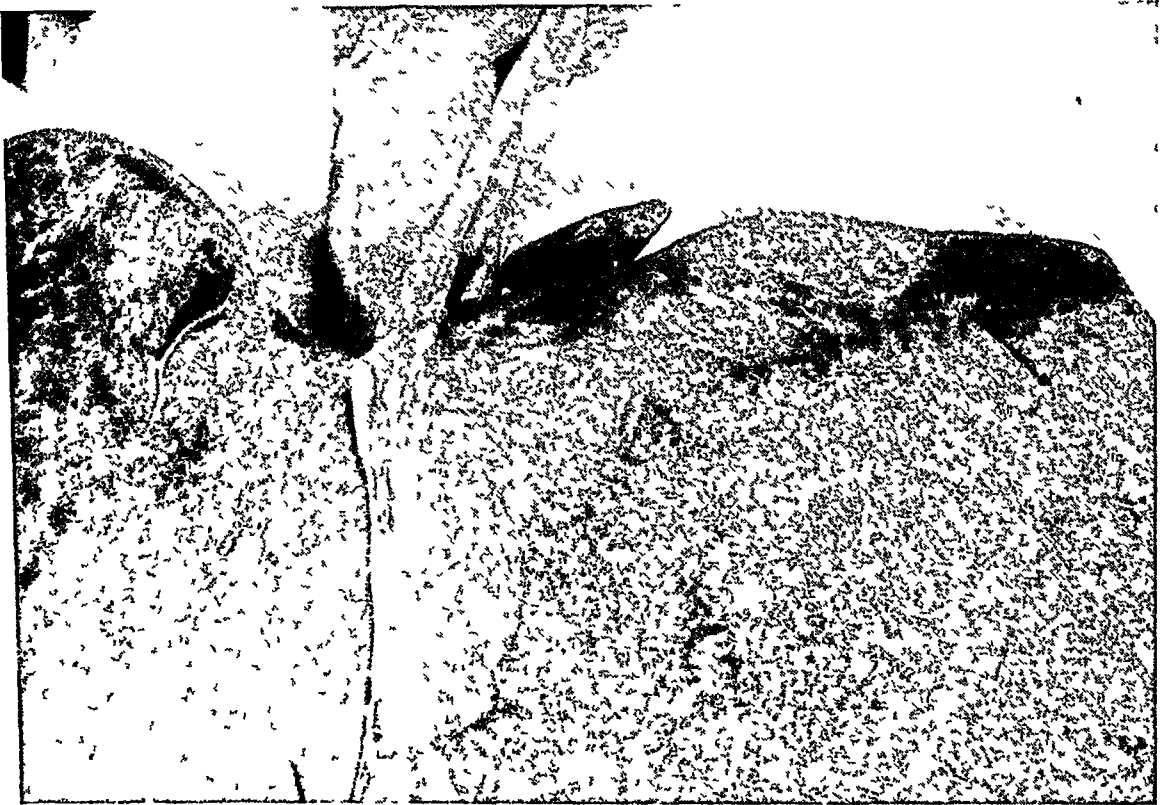


FIG 4 Closer view of liver, external and cut surface, as well as the umbilical vein

veins are widely patent throughout. The inferior mesenteric vein is also dilated and anastomotic channels can be seen to the hemorrhoidal veins. Collateral channels can be seen about the diaphragm extending toward the dilated azygos veins and similar dilated veins are present in the renal pedicle. Dilated short gastric and coronary veins are present extending laterally toward the dilated esophageal veins previously described. Short gastric veins cannot be followed within the stomach wall. Several dilated venous channels are seen within the hepato-duodenal ligament, but do not approach the point of cavernomatous transformation.

The spleen weighs 900 grams and measures 26 by 13 by 5 cm. Its smooth thin capsule is free of adhesions to the diaphragm, but a few fatty tags are present carrying rather large dilated veins. Surfaces made by sectioning are firm, pale, with prominent trabeculae and veins, and obscured malpighian follicles (figure 5). It is interesting to note the tortuosity and early sclerosis without atheromatous plaque formation of the splenic artery near the hilus of the spleen. No generalized lymphadenopathy is present.

The kidneys are of equal size, similar appearance, and together weigh 200 grams. Capsule strips with difficulty from a coarsely granular surface mottled yellow-brown to gray. Cut surface is firm with cortex reduced to about 3 mm in thickness and poorly demarcated from the medulla. Both are mottled yellow-brown to light gray with obscured markings. Vascular markings are rather prominent. Kidney pelves, ureters, and bladder are essentially normal. Prostate gland is of average size and is grossly normal.

The hypophysis was not examined. The thyroid and adrenal glands are grossly normal. Four parathyroid glands are found without difficulty, perhaps because of slight increase in size. A small fragment of thymic parenchyma is present in the fat pad.

Anatomical Diagnosis Cirrhosis of liver, undetermined type and etiology, with patent umbilical vein (Cruveilhier-Baumgarten syndrome), chronic congestive splenomegaly, recent gastric hemorrhage, chronic glomerulonephritis, cardiac hypertrophy, hypertensive, phlebosclerosis, portal vein, slight, arteriosclerosis, local, splenic artery, slight, and dilatation of esophagus, type undetermined.

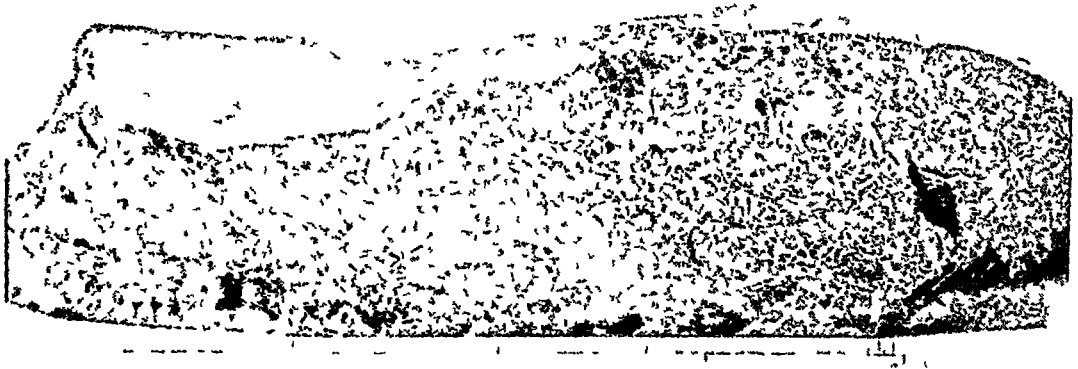


FIG 5 Spleen, showing increase in fibrous tissue and prominence in venous markings

Histological Examination Liver—Blocks were taken to study the microscopic appearance of the liver throughout the various divisions of the portal and hepatic veins. Blocks were taken of both the left and right branches of the portal vein near the hilus, and show some thickening of the wall, particularly of the intima. An increased amount of loosely arranged connective tissue surrounds the vein, and scattered through it are a number of lymphocytes. The hepatic ducts and artery in the same area show no significant changes. Repeated sections to show the successive subdivisions of the portal vein show the persistence of a varying grade of periportal fibrosis. Generally, it is confined to the periportal area and does not appreciably deform lobular architecture (figures 6 and 7). Microscopically it consists of rather loosely arranged collagenous fibers in which there are scattered lymphocytes, plasma cells and histiocytes. Within this connective tissue there is apparent proliferation of bile ducts and apparent increase in vascular channels. The portal vein branches appear everywhere somewhat dilated with slight thickening of their walls. Serial sections made to follow the course of the fourth division portal branches show no great deformity in the histography of the liver and no recognizable hypoplasia of the portal radicles. There are varying degrees of intrusion of the thickened peri-

portal connective tissue within the lobule, usually this is slight. In some places, particularly near the second and third divisions of the portal vein, there is complete isolation of portions of one or more lobules by such extension of connective tissue, thus producing the appearance of nodules. Nowhere do these nodular areas appear to consist of newly proliferating liver cells. In sharp contrast to this periportal fibrosis is the almost complete absence of scarring about the tributaries of the hepatic veins as

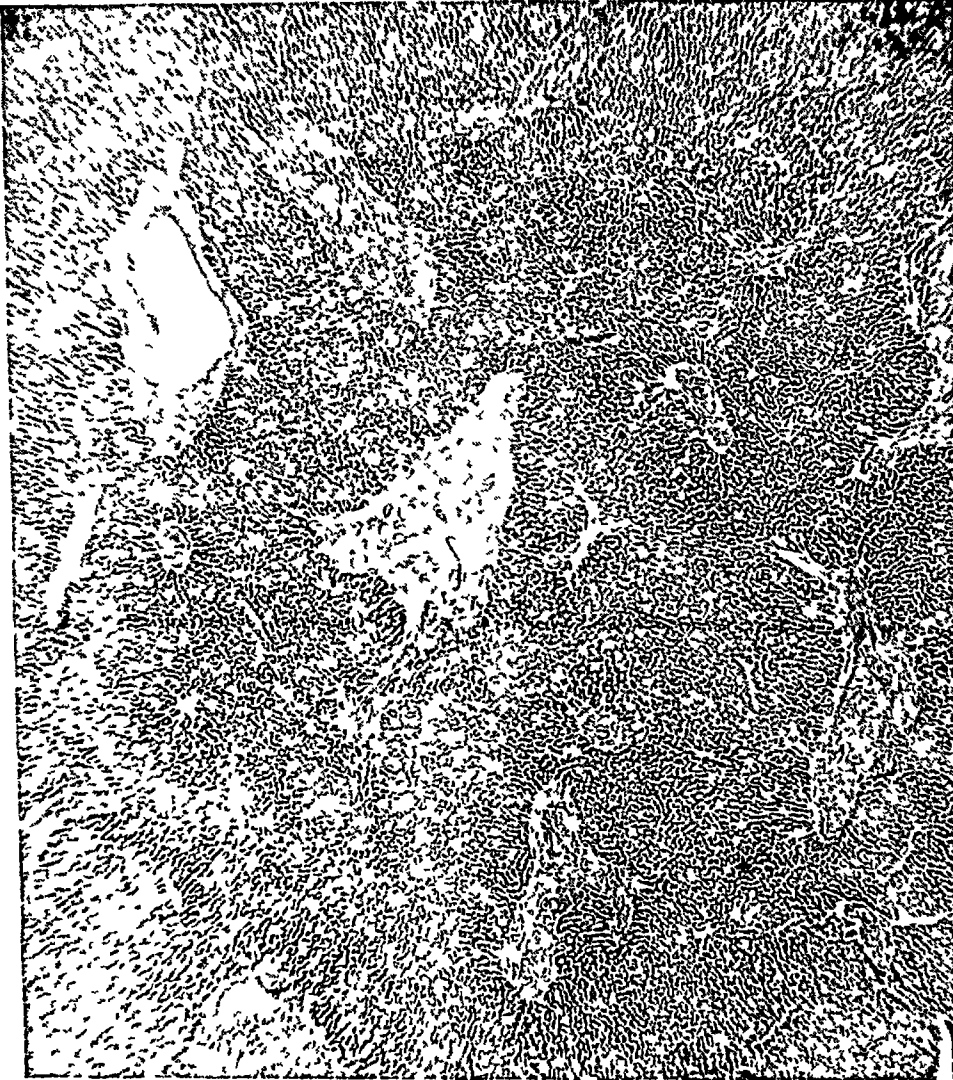


FIG 6 Liver at low magnification ($\times 15$) to show periportal scars without gross deformity of architecture

they are traced in various sections, beginning at the inferior vena cava. The interdigitations with the branches of the portal vein are fairly well preserved despite the fibrosis which is present. The liver cell cords are fairly well formed, most of the cells appearing smaller than normal and showing considerable fatty change, as well as cloudy swelling. Degenerative changes are also present in some of the nuclei. No bile staining is noted. The interlobular branches of the hepatic artery are prominent. With the Van Gieson stain the rather coarse periportal fibrosis is accentuated. The reticulum stain shows no particular changes within the liver lobules. Krajian stain reveals no spirochetes.

Umbilical vein—Sections were made from various portions of the wall and show a similar structure throughout. In most places differentiation into three coats is ill-defined. In the intima definite lining cells can be seen in some areas. Beneath these there is loosely arranged elastic and collagenous fibers. In the media the connective tissue is more firmly organized and scattered through it are fragmented smooth muscle fibers. This is confirmed in the Van Gieson stain. An edematous zone demarcates

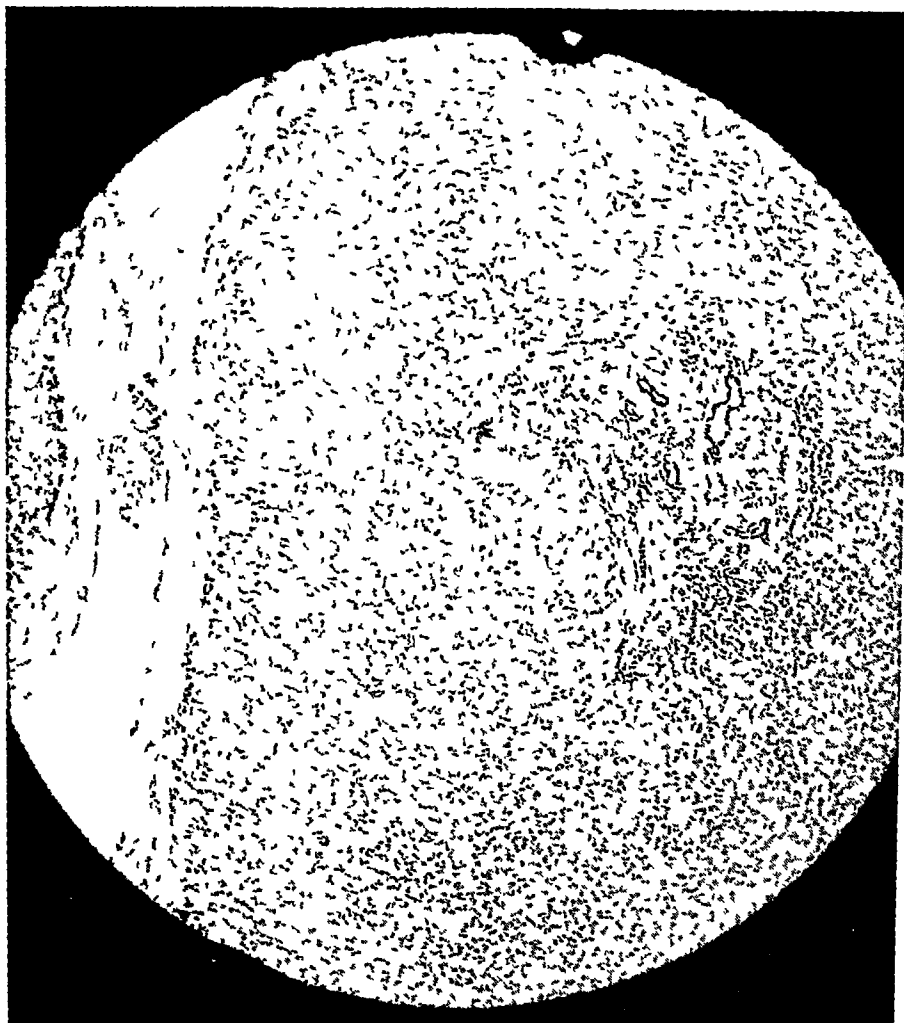


FIG 7 Liver showing periportal fibrosis and absence of scarring about hepatic vein ($\times 60$)

the adventitia which is thin and contains fine capillaries (figure 8). The histological appearance of the umbilical vein is similar to the normal control taken about the time of birth, showing early retrogressive changes, as described by Meyer¹¹.

Abdominal wall in the region of the umbilicus—Sections show many dilated veins, usually with thickened intima and patchy phleboscлерosis. These vessels are no doubt collateral communications with the umbilical vein. Of interest is the occurrence of loose areolar tissue containing inflammatory cells very similar to that seen about the portal vein at the hilus of the liver.

Spleen—The capsule and trabeculae are greatly thickened. The large venous channels are dilated and have thickened walls and increased surrounding fibrous tissue. The

bilical vein itself (with communication with the epigastric veins) and an atrophic liver, the result of hypoplasia of the portal system. It is inferred from Baumgarten's descriptions that a certain amount of fibrosis might be present, secondary to the atrophic state of the liver, but typical or advanced cirrhosis is not considered part of the picture.

As one attempts to examine critically the data concerning the cases reported in the literature it becomes apparent that many cases have been included on insufficient evidence. Others do not at all correspond to the criteria or descriptions of the original authors. Much of the confusion has been introduced by cases in which umbilical circulation played a prominent rôle but in which the umbilical vein itself was not involved. In other cases, the umbilical vein itself was involved but only secondary to some independent preexisting disorder. Before attempting a rational classification of the reported cases we wish to review briefly the rôle of the umbilical vein in portal circulation.

The development of the umbilical veins is closely related to the development of the portal system. In the early embryo the umbilical and vitelline veins are paired vessels and empty into the sinus venosus. As the liver parenchyma begins to form in the tissue of the septum transversum, there is interposed between these veins and the sinus venosum (later to form the atrium of the heart) a series of sinusoidal veins within the liver. These veins are formed by branching of the left umbilical and vitelline veins. The left umbilical vein also maintains a direct connection with the sinus venosum by means of the ductus venosum. The right umbilical vein disappears early. As the capillaries of the liver develop into their final state, the adult portal vein is developed from the vitelline veins and the left umbilical vein empties into the left branch of the portal vein and contributes to the sinusoids in the left lobe of the liver. Before birth most of the placental blood is shunted directly from the left umbilical vein to the atrium of the heart through the ductus venosum. The important rôle of the umbilical vein in the development of the portal system is well shown in figure 9 from Mall¹⁰. Baumgarten suggested that a congenital failure of the portal tree to develop would maintain umbilical vein patency and initiate the changes seen at autopsy, and be responsible for the clinical picture which the patients presented.

† After birth and ligation of the umbilical cord, the umbilical vein atrophies to form the ligamentum teres within the falciform ligament, which process occurs within two months following birth, and the ductus venosum forms the ligamentum venosum. However, the upper portion of the umbilical vein remains patent into adult life as the Rest-Kanal of Baumgarten. Other vestigial veins which may occur will be described below. Normally there is no communication between the umbilical and the epigastric veins in the abdominal wall. The vestigial remnants of the retrogressive changes in the umbilical vein have no functional significance unless some disease process leading to portal hypertension invokes the development of all available collateral channels.

As McIndoe¹⁷ has indicated, the collateral circulation following portal obstruction occurs in three general areas. The two most important areas are the anastomosis of portal tributaries with the terminations of the gastrointestinal tract, and the zones where the gastrointestinal tract or its appendages contact the retroperitoneal tissues or abdominal wall either through developmental relationship or pathological alteration. The third pathway of collateral circulation is through the obliterated embryologic circulation in the falciform ligament and is less frequently utilized. When this

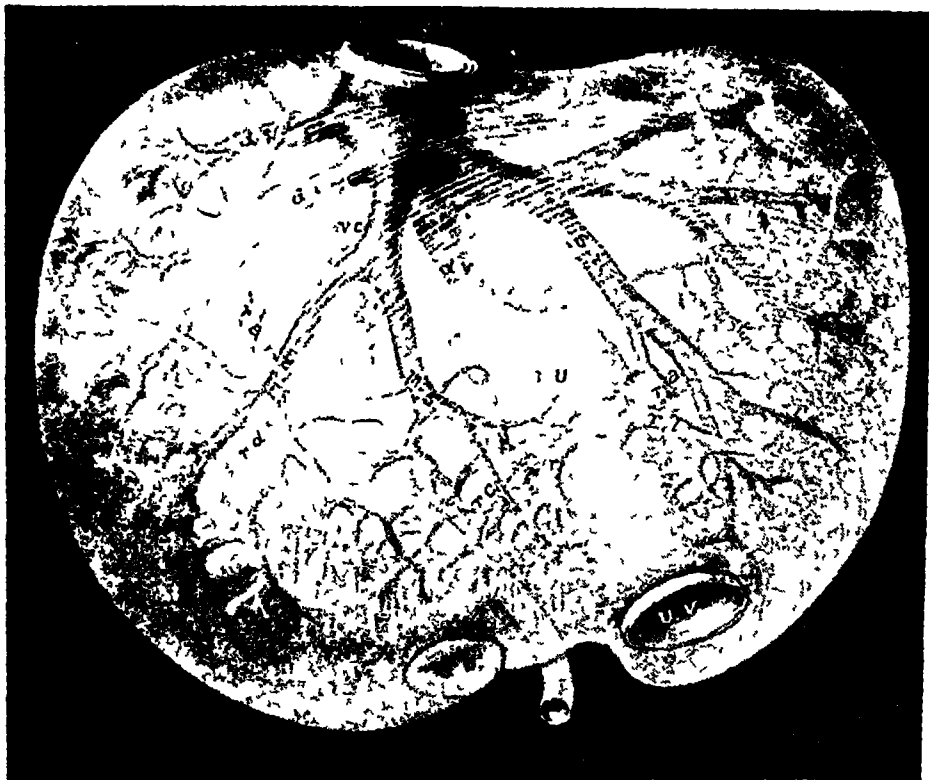


FIG 9 Showing relationship of umbilical vein to development of portal system (after Mall, Franklin P, American Journal of Anatomy, 1905, v, 266, reproduced through the courtesy of the Wistar Institute of Anatomy and Biology, Philadelphia, Pa, publishers)

pathway is utilized it is usually by anastomosis of the paraumbilical veins with the thoraco-abdominal veins. According to Weiss¹⁸ this parietal system of veins is derived from six superficial veins, and five deep veins. Of the latter, the epigastric veins are important.

According to McIndoe,¹⁷ the umbilical vein itself rarely participates in this collateral circulation, being "entirely obliterated a few days after birth." However, certain anatomic studies and dissections described in reported cases have established the existence of exceptions to this rule. We have previously alluded to the frequent patency of the terminal end of the umbilical vein in otherwise normal adults. This observation was made by Baumgarten¹⁹ in 60 autopsies, and confirmed by Robin²⁰. We have confirmed this occurrence

in several autopsies on children and adults with or without portal hypertension (figure 10) Plate 1 serves in part to illustrate the utilization of the Rest-Kanal in portal collateral circulation In figure 1, the communication is

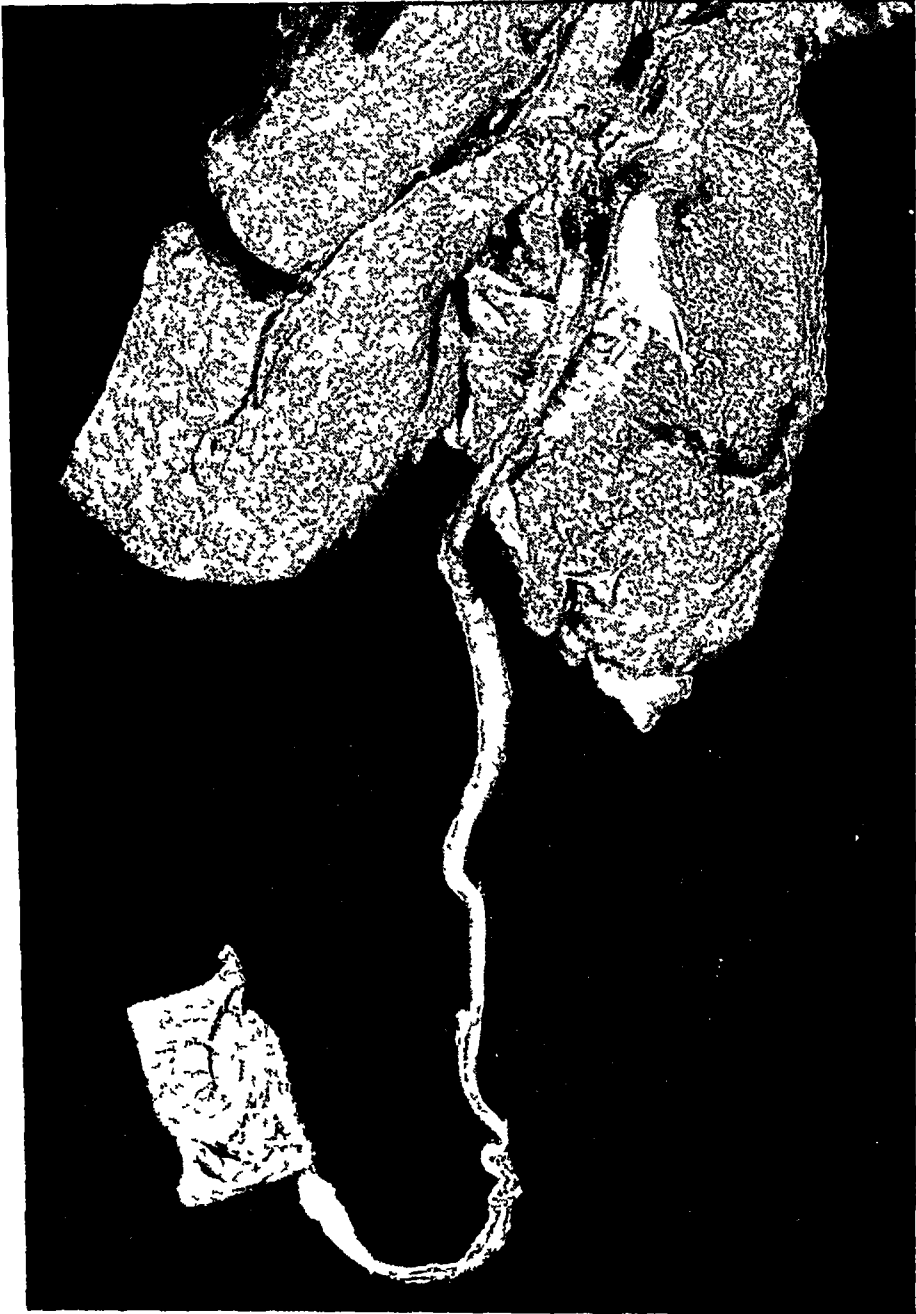


FIG 10 Male, aged 12, dying of toxic cirrhosis with portal decompensation A small Rest-Kanal was patent on injection The remainder of ligamentum teres obliterated despite the presence of portal hypertension early in life

by means of the vein of Burow (intercalary vein of Baumgarten) which runs peritoneally along the abdominal wall In figure 2 one or more of the paraumbilical veins of Sappey may be unusually large and connect the Rest-Kanal with the epigastric veins²¹ These run in the ligamentum teres

and not subperitoneally, as does the vein of Burow. Not pertinent to the present discussion, but also shown in figure 2, are the more frequent connections of the paraumbilical veins of Sappey from the epigastric to the portal vein or its tributaries^{22, 23}

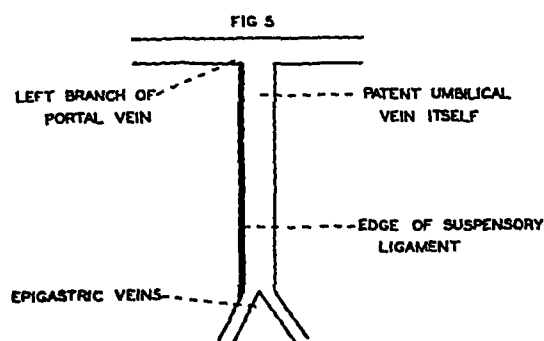
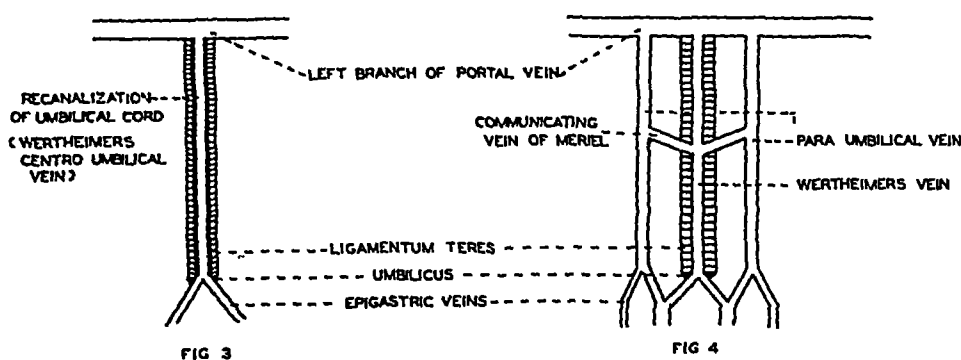
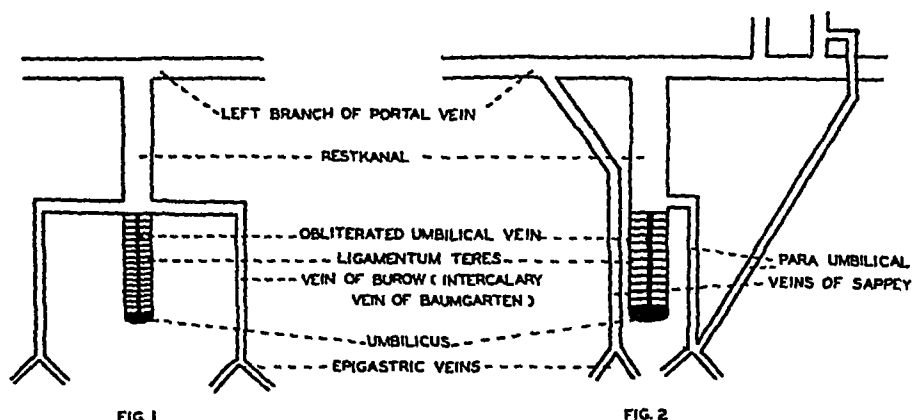


PLATE 1 Diagrammatic illustration of various reported means of utilization of umbilical vein in portal collateral circulation

In figures 3 and 4 of plate 1 there is illustrated another means of utilization of potential communications of the umbilical vein in portal collateral circulation. Wertheimer²⁴ reported recanalization of the umbilical vein within the ligamentum teres to produce communication between the epigastric veins and left branch of the portal vein. This is illustrated in figure 3. In

figure 4, the situation is complicated by communicating veins as described by Meriel²⁵ between Wertheimer's vein and the paraumbilical veins

Thus we see that in addition to the usual potential collateral connections of the paraumbilical veins with the thoraco-abdominal veins, there may occur

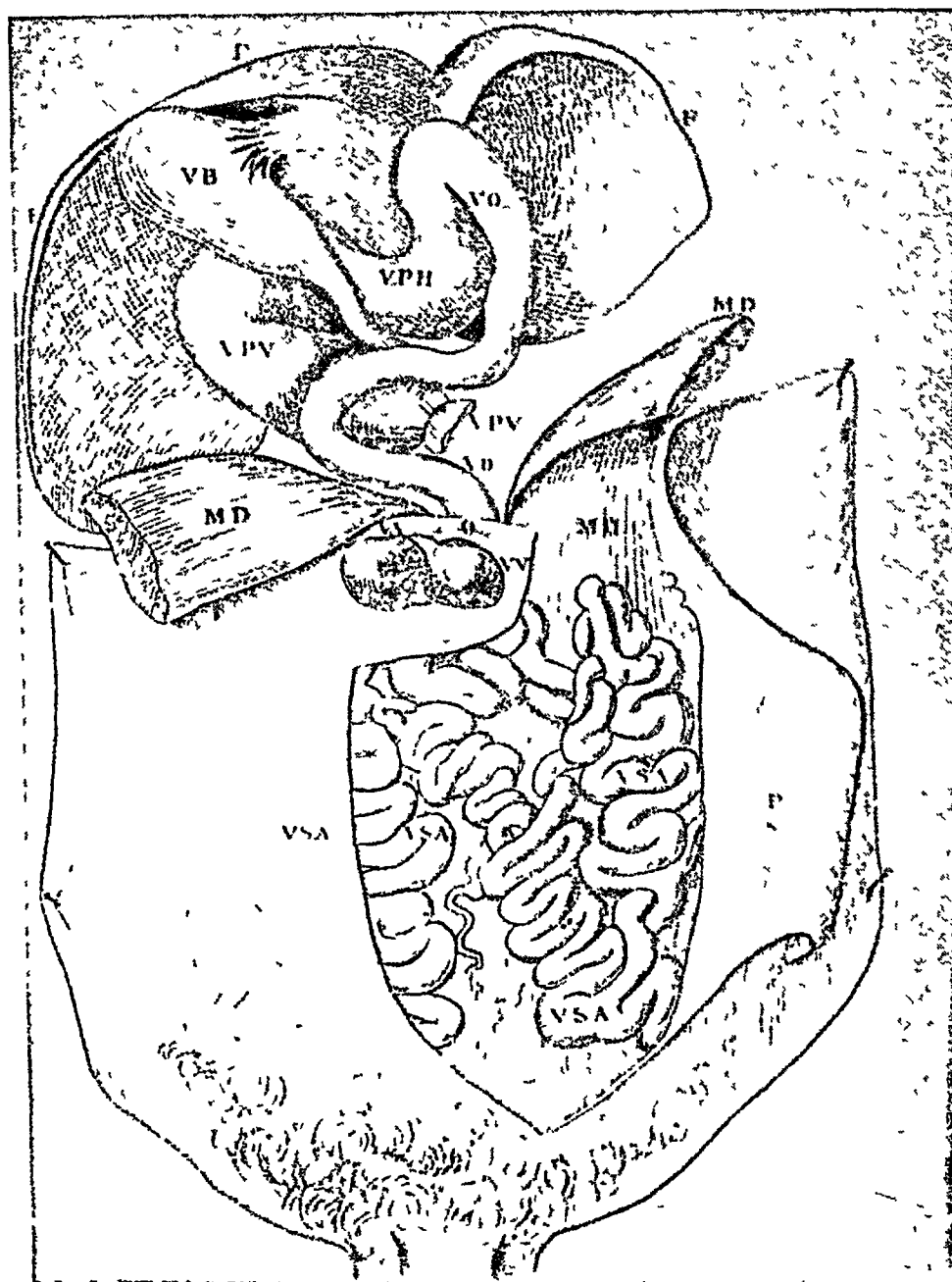


FIG 11 Reproduction of illustration by Cruveilhier of original case reported by Pegot and Cruveilhier

anastomoses of the latter veins through collateral channels furnished by the unobliterated portion of the umbilical vein itself. In either instance the excessive development of collateral circulation in this area in a patient with portal obstruction of whatever cause may lead to a clinical picture reported as an example of Cruveilhier-Baumgarten disease.

Finally, and most important in relation to this report, is the persistent patency of the umbilical vein itself. This is illustrated in figure 5 of plate 1. Here the vein is of the same size or larger than in fetal life and no ligamentum teres is present. It runs along the inferior margin of the suspensory ligament. Such a completely patent umbilical vein was first described as an incidental finding at autopsy by Manec²⁶ and Menière²⁷. The association of this finding with atrophy of the liver, large spleen, and portal decompression was first described by Pegot¹ and Cruveilhier².

We have thus elaborated the part played by the umbilical vein in portal circulation, and have shown its potential collateral connections in portal hypertension, apart from the more usual connections through the paraumbilical veins. We have already alluded to the contention that a congenital patency of the umbilical vein either alone (Cruveilhier) or associated with congenital hypoplasia of the portal system (Baumgarten) may constitute an individual disease entity. It also became apparent that any other disease resulting in portal hypertension which happens to utilize umbilical collaterals excessively, will produce a very similar if not identical clinical picture. The difficulties of classification of such cases is thus evident. Even the autopsy may not permit complete classification, since some of the changes seen, e.g., fibrosis or cirrhosis in the liver, might be secondary to maldevelopment of the portal system. However, if one takes into consideration the original concept of Cruveilhier and Baumgarten, together with the points already brought out in the discussion, the reported cases in the literature (table 1) can be roughly divided into the following groups:

1 Patency of the umbilical vein itself

A Associated with the other clinical and pathological findings as described by Cruveilhier and Baumgarten, cases 1, 7, 19, 21, 25, and our second case (case 55 in table 1)

Here there is a clinical picture of portal hypertension with excessive umbilical circulation, and necropsy reveals patency of the umbilical vein itself, atrophy of the liver with little or no cirrhosis and splenomegaly. Any hepatic fibrosis which may be present is thought to be secondary to atrophy associated with portal hypoplasia. The etiology is presumably congenital patency of the umbilical vein associated with hypoplasia of the portal system. In cases 1 and 2, the authors also list other factors of possible etiological significance:

B Associated with some independent disease of the liver or portal system resulting in portal hypertension, viz

1 Advanced portal cirrhosis, cases 24, 27, 42, 44, 46, 53

2 Anomaly or occlusion of the hepatic veins, cases 32 and 47.

In this group of cases the assumption is that some disease of the liver or portal system had developed in a patient who happened coincidentally to have available a congenitally patent umbilical vein. The latter then dominated

the collateral circulation and led to the clinical picture as seen in Group A. Case 53 is an interesting example of how portal hypertension at birth (the result of toxic hepatitis and cirrhosis) may have served to keep the umbilical vein patent. The cases of primary hepatic vein disease, despite the contentions of some of the reporting authors, are obviously quite different in origin from the original cases of Cruveilhier and Baumgarten. The coincidental existence of a patent umbilical vein has led to their being reported in this group. Some of the cases in Group I B where advanced portal cirrhosis is present, may perhaps be true cases of Cruveilhier-Baumgarten disease where the hepatic lesion has progressed to a severe grade of cirrhosis.

II Cases where there is some disease of the liver or portal system resulting in portal hypertension in which collateral circulation through the umbilical area *apart from the umbilical vein* plays a prominent rôle

A Cases of portal cirrhosis of the liver associated with unusually prominent paraumbilical veins, cases 2, 4, 6, 12, 26, 34, 50

This is the largest subgroup and is the probable situation in most cases of cirrhosis with loud venous hum, murmur, or marked caput medusae

B Excessively prominent paraumbilical veins with portal hypertension other than cirrhosis of the liver

Case 40, hypoplasia right branch of the portal vein, atrophy of liver, no cirrhosis, and patency of paraumbilical vein

C Patency of other collaterals in the umbilical area, in association with cirrhosis or other causes of portal hypertension

This refers largely to the utilization of collateral channels in the umbilical area furnished by remnants of the umbilical vein, as indicated in plate 1. The most frequent cause of the portal hypertension in these cases is cirrhosis of the liver

Examples

- 1 Case 16, cirrhosis of liver plus patent vein of Burow
- 2 Case 22, cirrhosis of liver plus patent Wertheimer's vein
- 3 Case 33, stenosis of hepatic vein orifices, together with patency of Wertheimer's (central) vein

III Cases with a clinical picture considered as Cruveilhier-Baumgarten disease, cirrhosis, etc., but without adequate necropsy confirmation. This is the largest group, comprising 30 cases, which can be divided into three subgroups, as follows

A Cases with the clinical picture of Cruveilhier-Baumgarten disease who were alive at time of report, cases 5, 8, 9, 13, 17, 18, 28, 29, 31, 35, 37, 38, 39, 43, 49, 51, 52, and our first case (53 in table 1).

B Cases with clinical picture of Cruveilhier-Baumgarten syndrome who had died but had not been necropsied, cases 15, 20, 36, 41, 45

- C Cases with clinical picture of Cruveilhier-Baumgarten syndrome which came to necropsy, but had inadequate description of the umbilical circulation, cases 3, 10, 11, 16, 23, 30, 48

Proper autopsy study in Group III would have led in most cases to classification in one of the other groups

We have thus outlined a classification of all cases that have been considered as having the clinical picture of Cruveilhier-Baumgarten syndrome, i.e., symptoms and signs of portal hypertension with evidence of excessive umbilical circulation in the form of a loud murmur or thrill. It is evident that the clinical picture dependent on portal hypertension associated with intense umbilical collateral circulation can be produced by a variety of etiologic factors combined with a variety of anatomical arrangements of the umbilical circulation. It is therefore impossible to limit the clinical diagnosis to any given group of pathological findings. To attempt to do so would introduce the same confusion as has resulted from attempting to delineate rigidly a case of Banti's disease according to Banti's clinicopathological criteria, the clinical aspects of which overlap with so many other conditions. It should therefore be recognized that any patient having portal hypertension, generally with splenomegaly, and in whom evidence in the form of visible veins, murmur and thrill of excessively prominent umbilical circulation exists, merits the diagnosis of *Cruveilhier-Baumgarten syndrome*. Further etiologic and pathogenic evaluation of the case will be dependent on the necropsy findings, especially in the liver, portal system, umbilical circulation. *Those cases which show at necropsy patency of the umbilical vein itself together with atrophy and little or no fibrosis of the liver would then be considered as examples of Cruveilhier-Baumgarten disease.* The term "Cruveilhier-Baumgarten cirrhosis" is undesirable since no particular type of cirrhosis has been proved to exist, and since, in fact, Cruveilhier and Baumgarten denied the importance of cirrhosis in the disease process.

Why then should the terminology "Cruveilhier-Baumgarten syndrome" be preserved? Why not consider these cases simply as examples of portal obstruction in which the umbilical collateral route has been used more abundantly than usual, such as the ordinary concept of caput medusae implies? We believe this designation should be preserved because

- 1 The clinical picture that includes intense umbilical circulation is rarely due to the use of ordinarily available collateral channels in the umbilical area. More likely, these findings signalize the existence of some unusual umbilical collateral as previously discussed, perhaps patency of the umbilical vein itself.

- 2 The small group of cases where the umbilical vein itself is patent constitutes a separate congenital anomaly. When this anomaly is combined with simple atrophy or minimal atypical cirrhosis, the theoretical proposals of Cruveilhier and Baumgarten of a separate entity to explain these cases must then be a consideration. Until such contentions are established or dis-

proved it should be worth while to segregate similar future cases in the literature under this title

3 Since it is impossible to distinguish the above group of cases from other disorders simulating them without careful autopsy examination (as indicated by cases reported in the literature) it becomes useful to designate the entire group as "Cruveilhier-Baumgarten syndrome"

Having thus outlined our concept of the nature of the Cruveilhier-Baumgarten disease, and shown the unfortunate need of incorporating these cases within a clinically indistinguishable group entitled Cruveilhier-Baumgarten syndrome we should like to recapitulate the essentials of the clinical picture of the Cruveilhier-Baumgarten syndrome. It may be possible to point out some minor differences helpful in distinguishing the smaller group of cases of Cruveilhier-Baumgarten disease.

The analysis of the reported cases indicates that the most frequent presenting symptoms, such as abdominal distention, digestive disturbances and hematemesis, are manifestations of portal hypertension. In general, the symptoms of the original disease causing the portal hypertension are usually absent or obscure. In the group of Cruveilhier-Baumgarten disease the age of onset of symptoms was less than in the whole group so that three of the five cases died before the age of twenty-five.

The principal physical findings, as indicated in the résumé of reported cases, are abdominal venous murmur and thrill, splenomegaly and dilated thoraco-abdominal veins. Caput medusae was mentioned by name in only four instances. Palpable liver was also a frequent finding during life (none enlarged at autopsy). Most of these signs are again related to the portal hypertension. The murmur and thrill are of most interest and diagnostic importance, since they depend directly on the venous anastomoses. They are usually loudest at the umbilical or epigastric regions, and generally continuous. The production of the murmur probably depends on the passage of blood to an area of different caliber or direction, or the eddying of current in a blind, dilated venous sac or pouch. The murmur might also be produced at points of constriction in the course of a dilated and tortuous vein. There is no apparent difference in the character of the murmur or thrill within the group of Cruveilhier-Baumgarten disease, although one might expect them to be most pronounced because of the larger size of the patent umbilical vein.

Splenomegaly is another fairly constant physical sign. Portal hypertension is common to all cases of the syndrome and contributes its share to the enlargement of the spleen in the form of chronic congestive splenomegaly. Other factors such as direct injury and irritative hyperplasia of the splenic reticulum may also be a factor in some of the cases. It is interesting to note that all five cases of Cruveilhier-Baumgarten disease have definite and frequently marked splenomegaly. The findings and problem with regard to the splenomegaly are similar to that of so-called Banti's dis-

case. Baumgarten's explanation of the spleen "taking over the function of the liver" is of course antiquated. He did, however, invoke portal hypertension as part of his explanation for the splenomegaly.

The leukopenia and secondary anemia reported in many of the cases are again probably related to the portal hypertension and splenomegaly. Positive blood Wassermann tests as evidence of syphilis occurred in approximately 15 per cent of the reported cases.

The clinical diagnosis most frequently made in the entire group was some form of cirrhosis of the liver. In 13 of the reported cases Cruveilhier-Baumgarten disease was suspected before death. In many instances the case was reported as such even when the autopsy findings did not conform to the original descriptions and criteria. The decision to consider a case clinically or pathologically as an example of Cruveilhier-Baumgarten disease may, in our opinion, frequently have been made because the physician or pathologist was impressed with the evidence of excessive umbilical circulation, without giving due critical attention to other necessary criteria.

PROGNOSIS AND TREATMENT

Most of the reported cases have died of portal decompensation or hepatic insufficiency. The duration of life after the clinical picture is established varies somewhat with the underlying cause of the syndrome. Some of the authors have contended that the widely patent umbilical vein would tend to delay the development of portal decompensation and diminish the frequency of gastric hemorrhage. However, in the group of Cruveilhier-Baumgarten syndrome, where the umbilical vein itself was patent the average age at death was 30.4 years as compared to 38.2 for the entire unselected group.

Since the clinical picture is usually dominated by progressive and usually fatal portal decompensation, the treatment consists largely of attempts to symptomatically alleviate this condition. Splenectomy is thought to be of no value and particularly contraindicated because of the danger of hemorrhage from the greatly dilated venous channels in the abdominal wall. Similarly, in doing paracentesis or peritoneoscopy great caution must be observed to avoid the large veins. Peritoneoscopy may be of value in demonstrating a large umbilical vein and in permitting biopsy of the liver in suspected cases of Cruveilhier-Baumgarten syndrome.

SUMMARY AND CONCLUSIONS

Our interest in the subject of Cruveilhier-Baumgarten disease was aroused by the two cases which we have presented. The data which we have been able to obtain from the original case reports of Cruveilhier and Baumgarten and of all subsequent reports have herein been reviewed. We believe that the term "Cruveilhier-Baumgarten syndrome" may be applied to patients having a clinical picture of portal hypertension featured by a loud

abdominal murmur and thrill The less important further details of this syndrome have also been enumerated Those cases that prove at necropsy to have the pathologic criteria as originally outlined should then be considered as examples of Cruveilhier-Baumgarten disease We believe our second case fulfills these criteria and becomes the fifth case of Cruveilhier-Baumgarten disease on record, and that our two cases increase the total number of reported cases of Cruveilhier-Baumgarten syndrome to date to 55 We believe the preservation of this name as applied to the syndrome is indicated because of the fairly uniform clinical picture centered about the loud murmur and thrill More important is the advisability of maintaining the integrity of a distinct disease of separate etiology and pathologic features, as delineated in the picture of Cruveilhier-Baumgarten disease We have therefore taken the liberty of reviewing the subject and of introducing in the English literature a new terminology for certain cases of portal system disease at the risk of creating similar confusion to that existing with regard to Banti's disease We believe, however, that an understanding of the original criteria will avoid such confusion and thus allow us to add to our diagnostic evaluation and understanding of certain patients presenting the clinical picture of portal hypertension

REFERENCES

- 1 PÉGOT Anomalie veineuse, Bull Soc anat de Paris, 1833 m-8, t vii, pp 108-109
Tumeur variqueuse avec anomalie du système veineux et persistance de la veine ombilicale, développement des veines souscutanées abdominales, Bull Soc anat de Paris, 1833, xlix, 57
- 2 CRUVEILHIER, J Traité d'anatomie pathologique générale, 1852, Chez J B Baillière, Paris (Vol II, viii classe, 3 ordre, p 315) Anatomie pathologique du corps humain, 1829-1835, Chez J B Baillière, Paris (Vol I, xvi^e livr, pl vi—Maladies des veines)
- 3 VON BAUMGARTEN, P Ueber Vollständiges Offenbleiben der Vena umbilicalis, zugleich ein Beitrag zur Frage des Morbus Banti Baumgarten Arbeiten, 1908, 6 (Arb a d geb d path Anat Inst zu Tubing, Leipzig, 1907, vi, 93-110)
- 4 HANGANUTZ, MARIUS Sur la cirrhose de Cruveilhier-Baumgarten, Presse méd, 1922, lxxiii, 20
- 5 GALIBERN, ANDRI Cirrhose de Cruveilhier-Baumgarten Thèse Université de Montpellier Faculté de Médecine, No 46, June 1935
- 6 THAYER, W S Of the presence of a venous hum in the epigastrium in cirrhosis of liver, Am Jr Med Sci, 1911, cxli, 313-327,
- 7 HENRY, J N Report of a case of loud venous hum heard over the xiphoid cartilage in cirrhosis of the liver, Am Jr Med Sci, 1912, cxliii, 72
- 8 WOLFAEGER, E E, and KITH, N M Epigastric thrill and murmurs in a case of cirrhosis of the liver with general vascular signs of arteriovenous fistula, Proc Staff Meet Mayo Clin, 1938, xiii, 33
- 9 MOSCHIKOWITZ, ELI Critique of Banti's disease, Jr Am Med Assoc, 1917, lxxv, 1045-1051
- 10 JOHNSON, JOHN M Relation of changes in the portal circulation to splenomegaly of the Banti's type, ANN INT MED, 1931, iv, 772-782
- 11 MEYER, A W Retrogressive changes in the fetal vessels and the suspensory ligament of the liver, Am Jr Anat, 1914, xxi, 477

- 12 BRATIANO, S, VISINEANO, N, and SALOMON, E Le syndrome (cirrhose) de Cruveilhier-Baumgarten, *Ann d'anat path*, 1929, *vi*, 293
- 13 BAINBRIDGE, F A, and LEATHES, J B The effect of arterial or venous obstruction upon the nutrition of the liver cells, *Biochem Jr*, 1907, *ii*, 25-33
- 14 FIESSINGER, NOËL, and PALMER, RAOUL G L'Alteration éloignée du parenchyme hépatique chez les chiens porteurs de fistules d'Eck, *Rev med de la Suisse Rom*, 1935, *lv*, 76-80
- 15 ROUS, P, and LARRIMORE, L D The relation of portal blood to portal maintenance, *Proc Soc Exper Biol and Med*, 1919-1920, *xxvii*, 65
- 16 MALL, FRANKLIN P A study of the structural unit of the liver, *Am Jr Anat*, 1905-1906, *v*, 227
- 17 MCINDOE, ARCHIBALD H Vascular lesions of portal cirrhosis, *Arch Path*, 1928, *v*, 23
- 18 WEISS, SAMUEL Diseases of the liver, gallbladder ducts and pancreas, Paul B Hoeber & Co, Inc, New York, 1935, p 387
- 19 VON BAUMGARTEN, PAUL Ueber das Offenbleiben foetaler Gefasse, *Centralbl f Med*, 1877, *xi*, 721
- 20 ROBIN, C Sur un point d'anatomie pathologique relatif a l'histoire de la cirrhose, par Sappey, *Bull de l'Academie Imperiale de Medecine*, 1858-1859, *xxiv*, 943-995
- 21 VON BAUMGARTEN, PAUL Ueber die Nabelvene des Menschen und ihre Bedeutung fur die Circulationsstörung bei Lebercirrhose, *Arb a d Geb d path Anat Inst zu Tübingen*, Leipzig, 1891, *i*, 1-46
- 22 VON BAUMGARTEN, PAUL Ueber das Nabelvene des Menschen, *Arbeiten von Tubingen*, 1891
- 23 EPPINGER, H, and RANZI, E Die Hepato-lienalen Erkrankungen Second Case, Julius Springer, Berlin, 1920, p 407
- 24 WERTHEIMER, R Recherches sur la veine ombilicale, *Jr de l'anat et physiol*, 1886, *xxii*, 1-15
- 25 MERIEL, E Note sur le systeme veineux para-ombilico-vesical, *Bull et mem Soc anat de Paris*, 1902, *6S*, *iv*, 469-471
- 26 MANEC, L Recherches anatomico-pathologiques sur la hernie crurale, Paris, 1826, *iii*-4
- 27 MENILRE, M Observations relatives à une anastomose remarquable du systeme veineux general avec le systeme veineux abdominal, *Arch de Med*, Paris, 1826, *4^{me} Année*, *x*, 381-388

ADDITIONAL BIBLIOGRAPHY

These are mostly tabulated and reported cases to which reference was not made in the text

- AUDRY, J Note sur les souffles veineux continues de la region sus-ombilical, *Lyon med*, 1932, *lxx*, 359-391
- BAMBERGER, H Granulirte Leber (Abstract) Carl Christian Schmidt's Jahrbucher der in- und auslandischen gesamten Medicin, Leipzig, 1851, *lxxii*, 195-197 (Original article in *Wien med Wchnschr*, 1851, No 1, p 6)
- BASTAI, R Aplasia delle vene suprahepatiche con persistenza delli vene ombilicale, *Poli-clinico (sez med)*, 1925, *i*, 1
- BENQUE, W Ein Fall von Persistenz der Vena umbilicalis mit anderen Anomalien, unter dem Bilde des Morbus Banti, *Wien klin Wchnschr*, 1912, *xxv*, 1249
- BORDONI, L Di una anastomosi fra la vene epigastrica e l'ombilicale nel feto umano, *Atti della Soc di Science Naturali di Pisa*, 1885
- BORDONI, L Nota clinica su di un caso di cirrosi epatica malarica (considerazioni sul soffio venoso epigastrico) *Atti Cong gen d Ass med ital* 1891, Siena, 1893 *xiv*, 151-154
Also—*Sperimentale*, Firenze, 1891, *lxxviii*, 433-437
- BOUVILLAUD—LE MAIRE Quoted by GAIIBERN⁵

- CATTI, GEORG Ueber Venengerausche bei der interstitiellen Hepatitis, *Ztschr f klin Med*, Berlin, 1907, lxi, 269-280
- CHABROL, E, and BERNARD, H Splénomégale par pyléthrombose, phlébite iliaque secondaire, *Bull et mém Soc méd d hôp de Paris*, 1928, lII, 9-12
- DAVIES, H (1863) Quoted by GALIBERN⁵
- FIESSINGER, NOEL, and BRODIN, PAUL Le syndrome ictéro-ascitique des hépatites scléreuses, *Presse méd*, 1924, xII, 121-123
- FIESSINGER, N, and MICHAUX, L A propos de la cirrhose de Cruveilhier-Baumgarten Deux cas nouveaux, *Bull et mem Soc méd d hôp de Paris*, 1930, xlvI, 88
- FIGUERIDO, ALVARO, and DE GONDRA, J M Cirrosis de Cruveilhier-Baumgarten, *Arch de Ap Digestivo*, Mayo, 1930 Cirrosis de Cruveilhier Baumgarten, *Arch de med, cir y espec*, 1930, xxxII, 197-201
- FLORAND, ANTOINE Souffles continus xyphoiden et sous-ombilical d'origine veineuse chez un cirrhotique (1), *Bull et mem Soc méd d hôp de Paris*, 1922, xlvI, 3d S, 1342-1346 Souffle continu au niveau de l'appendice xyphoïde, *Bull et mém Soc méd d hôp de Paris*, 1917, xli, 866
- FONTANEL, P, and PUIG, R Le souffle veineux paraxyphoidien et la cirrhose de Cruveilhier-Baumgarten, *Jr de méd de Lyon*, 1931, xII, 89
- FORNS, J S, and BARCELO, P Consideraciones Sobre la cirrosis de Cruveilhier-Baumgarten, *Rev de Barcelona*, 1935, xxIII, 411
- GIACCOMINI, C Sopra di un umpra comunicazione tra la vena porta a la vene ilache destre, *Giov d accad di Med di Torino*, 1873, 3 S, xIV, 587-621
- GALLAVARDIN, GRAVIER, and PUIG, R Bruit musical continu chez un cirrhotique Bruit derouet cave, *Soc med d hôp de Lyon*, 1928 (March 20)
- GAMBARATI, V Sopra un caso di soffio venosa udibile sull ala area epatica in individuo affecta da cirrosi epatica volgare, *Reforma med*, Roma, 1903, xIX, 153-156
- GINGOLD, NADOR Consideratiuni aspra sindromului Cruveilhier-Baumgarten Teza pentru Doctorat Bucuresti, 1929 (December 17)
- GUEZ, J A probable case of Cruveilhier-Baumgarten cirrhosis, *Tunisie Méd*, 1936, xxx, 138
- VON JAKSCH Ueber ein intra-abdominales Venensgerausch in Verlaufe der chronischen interstitiellen Leberentzündung, *Prager med Wchnschr*, 1895, xx, 13-14
- KAUFMAN, E Un cas de cirrhose de Cruveilhier-Baumgarten, *Monde médical*, N 755, 1929 (September 1)
- LUPU, N G, and GINGOL, N Un cas de syndrome de Cruveilhier-Baumgarten Quelques considerations sur la pathogénie de ce syndrome, *Bull et mém Soc méd d hôp de Bucarest*, 1929, I, 271-278
- LUTENBACHER, R Bruits de souffle veineux et cirrhose de Laennec (cirrhose de Cruveilhier-Baumgarten), *Presse med*, Paris, 1936, xlv, 847
- MASUDA, NIRO Ueber einen Fall Morbus Banti bei vollstandingem Offenbleiben der Vena umbilicalis, *Med Klin*, 1911, viI, 104-106
- MOUKTAR, AKIL Souffle continu, xyphoïdien au cours d'une pylephlebite, *Soc méd d hôp de Paris*, 1924, 3d Series, xlvIII, 572-575
- OETINGER, W, and MARIE, R-L De la maladie de Banti, *Rev de méd*, 1911, xXXI, 345-363
- PAGNIEZET and RIVOIRE Un cas de cirrhose de Cruveilhier-Baumgarten, *Soc med d hop de Paris*, 1929 (December 20)
- PIAZZA-MARTINI, V Del rumore di soffio venoso udibile sull'area epatica, *Riforma med*, Napoli, 1894, x, 663, 673, 687
- PICCHINI, L Contributo allo studio del soffio e fremito epigastrico nella cirrosi epatica Segno Firenze 1890-1891, I, 326-364 il Segno, fasc 12
- POPPIR, M Sur un cas de syndrome de Cruveilhier-Baumgarten, *Bull et mém soc méd d hôp de Bucarest*, 1923-1924, I-VI, 244-248
- RAOLI-DUAL, PH La cirrhose de Cruveilhier-Baumgarten Etude anatomique, clinique et classification symptomatique, *Thèse Paris*, 1931

- ROILESTON, H D Diseases of the liver, etc 1905, W B Saunders, Philadelphia, p 238
- SAPPEY, C Recherches sur quelques veines portes accessoires, Compt-rend Soc de biol, 1859, 3d Series, I, pt 2, 3-13
- SCHEELE, L Ueber einige seltene Nonnengeräusche und ihren diagnostischen Wert, Internat Beitr z inn Med, Berlin, 1902, II, 41-58
- SPINELLI, A, and PANA, C Occlusione delle vene sovraepatiche con oblitterazione della vena cava inferiore e di tutte le sue collaterali, con persistenza della vena ombelicale (sindrome di Cruveilhier-Baumgarten) e ginecomastia, Riv di clin med, 1934, XXXV, 499-551
- TAYLOR, F Cases of cirrhosis of the liver in children with some remarks on cirrhosis, Guy's Hosp Rep, 1895, III, 45-75
- TROUSSFAU, A, and SAPPEY, C Quoted by GAMBIRN⁵
- VISINEANO, N Contributiiuni la studiul sindromului Cruveilhier-Baumgarten Un caz prin anomalie portala si persistenta venei paraombilicale, Teza Bucuresti, 1928

CASE REPORTS

ACUTE HEMOLYTIC ANEMIA, AUTOAGGLUTINATION, TOXIC HEPATITIS AND RENAL DAMAGE FOLLOWING SULFATHIAZOLE THERAPY; CASE REPORT *

By ISADORE ROTHSTEIN, M D , and SIDNEY COHN, M D , *Bronx, New York*

SOON after the introduction of sulfanilamide into this country reports of various toxic manifestations following its use began to appear, among them reports of acute hemolytic anemia. Acute hemolytic anemia due to sulfanilamide administration was first described by Harvey and Janeway¹ in 1937 and since then has been noted by many other observers. In a large series of cases the incidence of this complication following sulfanilamide has been estimated as approximately 2.5 per cent of all adults and 8.5 per cent of all children receiving the drug.² Later studies have revealed an incidence of 1.8 per cent in all patients.³ Hepatitis as a toxic reaction to sulfanilamide was first described by Bannick, Brown and Foster in 1938.⁴ In the following year, Antopol and his associates reported two cases of acute hemolytic anemia following sulfanilamide therapy in which autoagglutination of the blood was present.⁵ We have not as yet encountered further reports of the latter complication of sulfonamide therapy. In 1940, Spring and Bernstein reported two cases from this hospital in which there was a coexistence of toxic hepatitis, acute hemolytic anemia and renal damage following sulfanilamide therapy.⁶ They noted that up to that time there was only one doubtful case reported with this combination of complications. Acute hemolytic anemia following sulfapyridine administration has been reported,⁷ and its incidence appears to be less than that of sulfanilamide.⁸

Sulfathiazole (2-para-aminobenzenesulfonamidothiazole), the thiazole analogue of sulfapyridine, was introduced by Fosbinder and Walter⁹ in August of 1939, and by Lott and Bergheim shortly thereafter.⁹ Experimental investigations by Van Dyke, McKee and others indicated that the new drug was of approximately the same order of toxicity as sulfapyridine.^{10, 11} During the past year many investigators who have used sulfathiazole in the chemotherapy of bacterial infection have become convinced of its efficacy in staphylococcic, pneumococcic and gonorrheal infections, and as a result of these clinical trials the drug is now generally considered to have comparatively low toxicity. A review of the literature, which is too lengthy to be summarized in a paper of this type, reveals no cases of acute hemolytic anemia in man due to sulfathiazole as far as we could ascertain, although a few instances of moderate anemia have been men-

* Received for publication February 25, 1941.

From the Departments of Pathology and Medicine, The Bronx Hospital.

Grateful acknowledgment is made to Dr. Joseph Felsen, Director of Laboratories and Research, for his valuable suggestions and to Dr. Henry Schumer, Attending Physician, for permission to use this case.

tioned. The case to be reported is one of acute hemolytic anemia, autoagglutination, toxic hepatitis and renal damage following sulfathiazole therapy in a pneumococcus type VII lobar pneumonia with recovery.

CASE REPORT

J. K., aged 45, white male, a tailor by occupation, was admitted to the medical service of Dr. Henry Schumer, The Bronx Hospital, on November 18, 1940, with a chief complaint of persistent chills and fever of three days' duration. He had felt entirely well until November 15, at which time he felt a draft and noted a stiffness of the neck. He also felt a pinching sensation in the left infrascapular region and about the left ear, lasting several minutes at a time. Toward evening there were chilly sensations, fever and anorexia. On the following day the patient had two series of severe chills, with a fever of 105° F. On the day before admission hoarseness developed, and there was one episode of vomiting. Chills and high fever continued, and hospitalization was advised.

The past history was negative except for an inflammation of the left eye due to a foreign body. The patient had been in this country for 20 years.

Physical examination revealed a fairly well-developed and nourished male who appeared acutely ill and dyspneic. The right eye was normal. The left eye was capable of perceiving only light and the pupil was fixed in mid-dilatation. The left fundus oculi showed evidence of secondary optic atrophy. The teeth were in poor condition, and the tongue dry. The lungs revealed dullness, increased fremitus, bronchophony and bronchial breath sounds over the left lower lobe with occasional medium moist râles. The blood pressure was 116 mm Hg systolic and 74 mm diastolic, and the pulse rate 140. The heart sounds were fair and no adventitious sounds were present. The abdomen and extremities were normal.

The admission diagnosis was lobar pneumonia of the left lower lobe and amblyopia of the left eye, probably on the basis of an old inflammation following implantation of a foreign body.

Clinical course. The patient's temperature on admission was 105° F, and chemotherapy was withheld because of a rapid drop of the temperature to 102.6° F, thus being interpreted as a possible sign of spontaneous resolution. However, on the next day, the temperature again rose to 104° F. The patient became suspicious of all physicians and attendants and cried out that he was "going to die" and that "food was being forced on him to poison him." His condition was interpreted by the consulting psychiatrist as a borderline toxic psychosis of the paranoid type. Sulfathiazole therapy was begun that evening with an initial dose of 2 grams, followed by 1 gram doses every four hours for the next 48 hours, a total dose of 17 grams being administered. The temperature during this time fell by rapid lysis and was normal for 12 hours before the drug was discontinued.

The admission blood count showed a hemoglobin of 94 per cent Sahli (13.6 grams), and the erythrocytes numbered 4,900,000 per cu mm. There was a leukocytosis of 16,000, with 56 per cent neutrophils, 33 per cent band forms, six lymphocytes, four monocytes, and one Turck cell. The urine was negative. The sputum was sanguinous and mouse inoculation revealed pneumococcus type VII. Roentgen-ray of the chest at the bedside exhibited pneumonic consolidation of the left lower lobe. The blood chemistry was normal, and the blood culture was sterile at the end of 144 hours' incubation. The blood Wassermann and Kahn tests were both three plus positive.

Forty-eight hours following the onset of the psychosis, the sensorium was clear, and the patient was well-oriented and cooperative. The psychiatrist found him en-

tinely recovered mentally. The chest signs showed clearing, and the patient was thought to be recovering.

However, on November 24, the seventh hospital day, the temperature rose suddenly from normal to 103° F. On the following day the temperature varied between 101° F and 102.2° F and the chest signs, i.e., dullness, bronchial breathing and bronchophony extended anteriorly and higher posteriorly. This was thought to indicate an extension of the pneumonic process, and sulfathiazole therapy was resumed in the same dosage (one gram every four hours). Radiograph of the chest at this time showed clearing of the pulmonary process. Temperature and pulse continued to be elevated. The sputum was now negative for type-specific pneumococci and also tubercle bacilli. By the twelfth hospital day, November 29, the blood sulfathiazole concentration had risen to 8.0 mg per cent.

Despite this high sulfathiazole level, severe chills and spiking fever up to 105.4° F occurred during the next two days, November 30 and December 1. Type VII anti-pneumococcal rabbit serum was then given in two divided doses without reaction, the total dosage being 108,000 units. Blood culture done at this time was sterile. Following the serum therapy, the fever dropped to about 102° F for the succeeding two days, December 2 and 3. The hemoglobin at this time had fallen slightly to 82 per cent and the leukocytes to 11,900 per cu mm. On the afternoon of December 3, the temperature rose to 103.4° F and the sulfathiazole was discontinued as this was thought possibly to be a drug fever. Following this, the temperature rapidly fell to normal. The total amount of sulfathiazole administered was 65 grams during a two-week period. (The drug was temporarily discontinued during the latter half of the first week of therapy.) The blood level at this time was 3.1 mg per cent. The chest findings continued unchanged and indicated persisting consolidation of the left lower lobe.

During the evening of December 4, the seventeenth hospital day, it was noted that the urine was red in color. On the following morning the patient complained of marked weakness, and the temperature which had been normal for eight hours rapidly rose to 102° F. On examination, the patient was in poor condition and had a thready pulse with a rate of 130/min. He was markedly stuporous, barely responded to stimuli, and there was clear-cut jaundice of the skin and sclerae. The liver was tender and enlarged to two fingers'-breadth below the costal margin. The skin was cold and wet, and the respirations were shallow and 40/min. The urinalysis had been repeatedly negative except for an occasional one plus albumin. Now the urine showed three plus albumin and was reddish-brown in color. The benzidine test was strongly positive and bile was doubtfully positive. The sediment showed no formed elements. The blood count showed a hemoglobin of 30 per cent, erythrocytes 1,790,000, platelets 590,000, leukocytes 65,800 with neutrophils 36 per cent, band forms 24 per cent, young forms 5 per cent, myelocytes 6 per cent, premyelocytes 3 per cent, plasma cells 4 per cent, lymphocytes 16 per cent and monocytes 6 per cent. The erythrocytes exhibited anisocytosis and a considerable amount of microspherocytosis. There were three nucleated red cells per hundred leukocytes. The icterus index was 37.5, the van den Bergh direct-immediate, and 1.5 mg of bilirubin per 100 cc of serum. The blood urea nitrogen rose to 40 mg per cent, and the non-protein nitrogen to 60 mg per cent. No sulfathiazole was present in the blood.

An intravenous infusion of 5 per cent glucose in saline was begun, and arrangements were made for an immediate transfusion. The patient's blood showed marked autoagglutination upon typing. After thoroughly washing his red cells in saline, he was found to have type A (Landsteiner) blood. In crossmatching with prospective donors the same difficulty was encountered. The patient's plasma and serum agglutinated the red cells of all four blood types as shown in figure 1. In view of the critical condition of the patient, it was deemed advisable to transfuse him with Type A

TABLE I

	11/18	11/29-30	12/2-3	12/5	12/6	12/7	12/9	12/11	12/12-13	12/16-17	12/19-21	12/23-24	12/26-27	12/30	1/9
<i>Blood</i>															
Hemoglobin (Sahl) %	94	92	82	30	50	18	52	78		78	75		76		80
Hemoglobin grams %	13.6	13.3	11.9	4.4	7.3	7.0	7.5	11.3		11.3	10.8		11.0		11.6
Erythrocytes millions/cu mm	4.9	4.7	4.2	1.79	1.92	2.5	2.83	1.3		3.7	3.86		1.2		3.96
Nucleated red cells per cu mm	0	0	0	2,000	3,000	4,400	530	1.3		260	0		0		0
Leukocytes per cu mm	16,000	22,900	11,900	65,800	55,200	67,400	27,800	14,600		13,200	13,200		10,500		9,700
Neutrophils %	56	86	83	36	42	61	68	75		59	59		65		63
Band Forms %	33	1	1	24	28	7	5	2		21	5		0		1
Young Forms %	0	0	0	5	8	10	8	1		0	0		0		0
Myelocytes %	0	0	0	6	6	5	8	0		0	0		0		0
Premyelocytes %	0	0	0	3	0	13	0	0		0	0		0		0
Lymphocytes %	7	9	9	16	7	13	8	14		15	28		29		33
Monocytes %	4	4	7	6	5	3	3	8		5	8		6		3
Plasma cells %	0	0	0	4	4	1	0	0		0	0		0		0
Reticulocytes %								4.0		1.4	0.8				
Platelets per cu mm				590,000	1.9	2.8	11.2		1.8		0.8		110,000		210,000
Mean corpuscular thickness, micr				42-36	3.1	460,000	300,000				130,000				
Fragility test % saline							1.16								
Heterophilic antibody test															
<i>Blood Chemistry</i>															
Icteric index															
Van den Bergh direct															
Serum bilirubin, mg %	12.7			37.5	26.3	15	8.9		5.8				12.0		
Urea nitrogen, mg %				1.5	biphasic	delayed	delayed		0.25				14.6		
Non-protein nitrogen, mg %				40.0	1.0	0.6	0.4	24.4	15.7				35.9		
Cholesterol, mg %				60.0	33.4	16.7	16.3	51.6	38.7				200.0		
Cholesterol esters, mg %					61.2	31.2	38.9	158.3					125.0		
Total proteins, gm %					137.5			100.0					6.29		
Albumin, gm %					75.8			5.34					3.69		
Globulin, gm %								2.75					1.84		
Fibrinogen, gm %								2.59					0.76		
Sulfathiazole conc., mg %		8	3.1	0				0							
<i>Urine</i>															
Appearance	clear		clear	red	red	sl red	clear		clear	clear					
Albumin	±		+	++	++	++	0		+	+					
Bile	0		0	±	0	0	0		neg	0					
Benzidine	neg		neg	++	++	+	neg		neg	neg					
Urobilinogen dilution of serum				neg	1125	debris	neg		neg	neg					
Microscopic					2-4RBC										
					3-6WBC										
					renal										
					cells and										
					casts										
					pos	pos									
Heller test for hgb			++++	++++		neg									
<i>Miscellaneous</i>															
Hippuric acid synthesis, gm							1.0		1.0	1.65	85%	2.12		1.5	2.79
Bromsulphalein test 30 min									55%		2.46			5%	
Galactose tolerance test, gm														neg	
Spinal tap														neg	
Blood Wassermann															
Blood Wassermann and Kahn tests															
Donath Landsteiner test	+++		++++	++++											
Cold (provocative) test															
Blood transfusions cc				1,000	500	500	500								

blood slowly by the citrate method. He received 1,000 c c of citiated blood that day without reaction, and there was striking improvement in his general condition.

On the following day, December 6, there was much improvement in the general condition of the patient. The jaundice was less marked, and there was no drowsiness or stupor. The liver was now only one finger's-breadth below the costal margin. The urinary output was satisfactory. The laboratory findings (summarized in table 1) indicated a lessening of the anemia, decreasing jaundice, marked immaturity of the

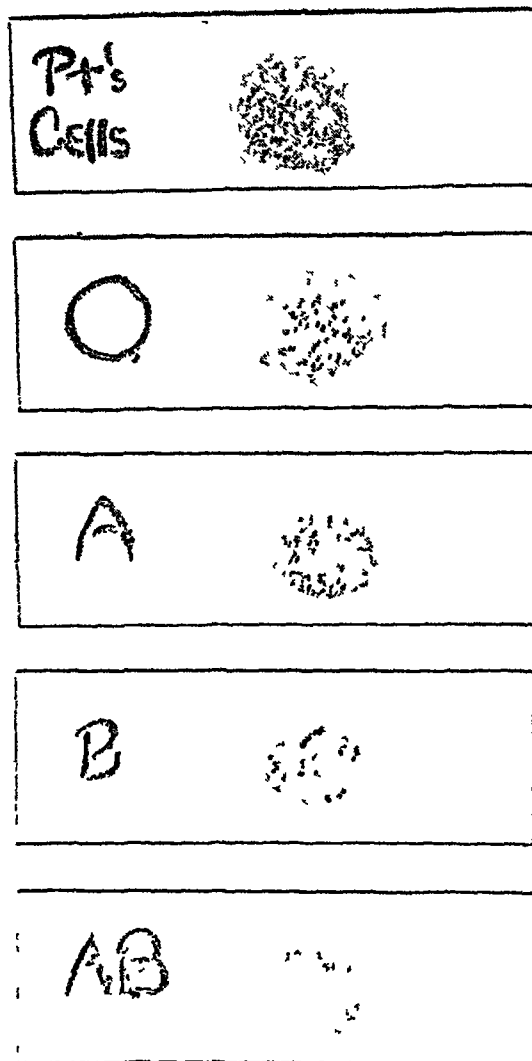


FIG 1 Autoagglutination and panagglutination exhibited by the patient's serum

erythrocytes and granulocytes, persistent hemoglobinuria, cellular evidence of renal damage, increased urobilinogen in the urine, and poor liver function. The Heller test (precipitation of blood-red stained urinary phosphates by means of alkali and heat) was positive and indicated the presence of hemoglobin in the urine. Spectroscopic examination was not done.

The patient received three more transfusions of 500 c c of citrated blood, the dates being December 6, 7, and 9. Autoagglutination and panagglutination were still present during the last crossmatchings on December 9, and persisted for several days thereafter. By that time the jaundice, hepatomegaly and hemoglobinuria were gone. There was

steady clinical improvement despite a fluctuating temperature and slowly resolving pneumonia. Tests of hepatic function, such as bromsulphalein, hippuric acid synthesis, blood cholesterol and proteins, showed significant changes. Even at the time of discharge on December 31, not all of these tests had returned to normal figures. The azotemia, however, had disappeared by this time. On December 12 the mean corpuscular thickness was normal and spherocytes were no longer seen.

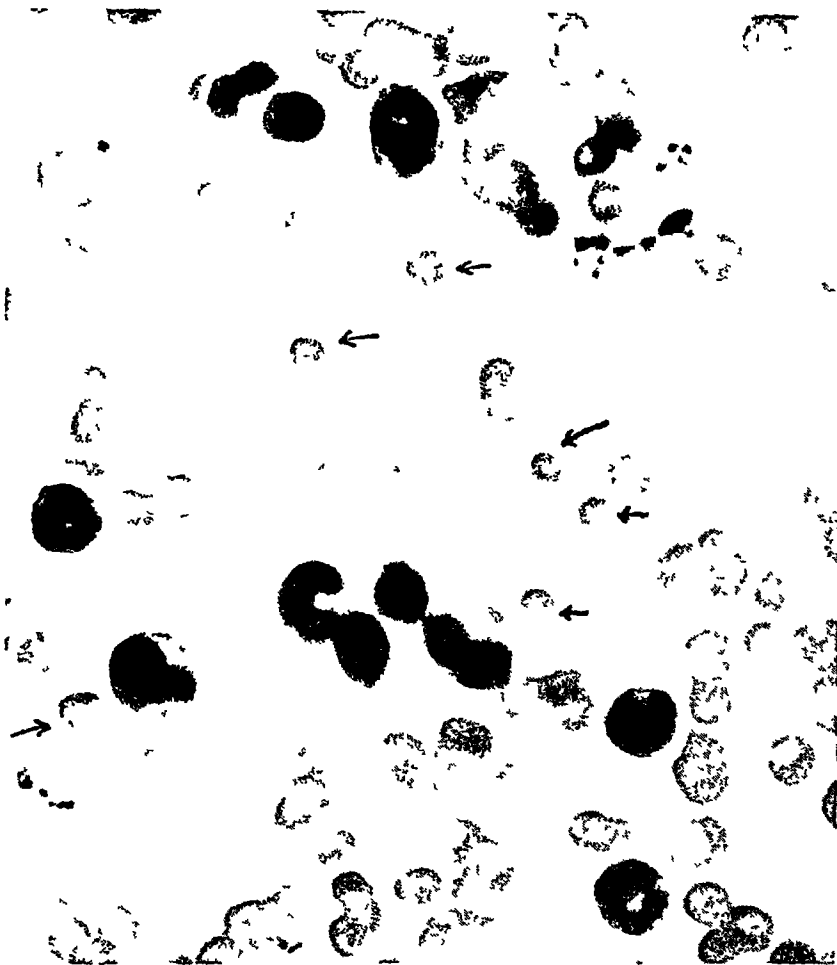


FIG 2 Peripheral blood smear showing a number of microspherocytes

On the day of discharge, December 31, the patient felt well, and although there was clinical and radiographic evidence of a small but definite area of unresolved pneumonia in the left lower lobe, the patient was discharged from the hospital.

The patient returned on January 9, 1941, for a check-up before going to a convalescent home. At this time, which was 35 days after the onset of the acute hemolytic episode, there was still a moderate anemia present despite continuous iron therapy. Examination of the lungs showed a patch of dullness, increased fremitus and bronchial breathing, though decreased in extent, at the inferior angle of the left scapula. The hippuric acid synthesis at this time was slightly below normal.

COMMENT

During the time that the patient's blood exhibited panagglutination the clumps of red blood cells on the blood typing and crossmatching slides could not be

broken up by the addition of a drop of physiological saline. Experiments were conducted with the patient's blood on December 5 to determine the titer of these agglutinins. Saline dilutions of the patient's serum were mixed on glass slides with suspensions of the patient's washed red cells, type O cells, type A cells and sheep cells. The agglutinins, however, were found to be present in low titer as complete agglutination occurred in all cases with 1:2 dilutions of serum and rouleaux formation with the 1:4 dilutions. Rabbit cells were agglutinated in a dilution of 1:128 but this was found to be due to a species agglutinin found in all types of human blood.

On December 9, the Donath-Landsteiner test was performed and was negative. The patient's serum of that day and a 5 per cent suspension of his washed red cells were then incubated in the serological test tube at 37° C for 24 hours. No hemolysis occurred. The patient's packed washed red cells were kept under the same conditions in a 10 mg per cent saline solution of the sulfathiazole he had received for treatment, and there was no hemolysis. When this concentration of sulfathiazole was produced experimentally in a sample of his serum and incubated in a similar manner with his packed washed red cells, there was no hemolysis. High concentrations of rabbit testing serum and the type VII antipneumococcus rabbit serum he had received for treatment were then produced in saline and in the patient's own serum. When these were placed in contact with the patient's packed washed red cells under like conditions, no hemolysis was noted. In other words, no autohemolysis could be demonstrated experimentally *in vitro*. Also, sulfathiazole and antipneumococcus type VII rabbit serum did not produce hemolysis of the patient's blood *in vitro*.

On two occasions a cold provocative test was done in which the patient's hands were immersed for 15 minutes in ice water at 5° C. All urine specimens were saved for the following nine hours, and there was no evidence of hemoglobinuria.

In reviewing this case, there are several interesting points which should be mentioned. There was a rapid satisfactory clinical response following the first administration of sulfathiazole. Within 48 hours the temperature had dropped to normal and the patient felt much improved. However, the pulmonary signs of consolidation were entirely unchanged in spite of this clinical improvement and resolution of the pneumonic process required several weeks. The toxic delirium or psychosis exhibited by the patient preceded the commencement of specific chemotherapy and it rapidly disappeared as the clinical condition improved, presumably as a result of sulfathiazole administration. It evidently was not an example of the occasional neurological or psychiatric manifestations incident to sulfonamide therapy. The chemotherapy was discontinued because of the suspicion of a drug fever, and the first indication of a toxic reaction was the red urine that the patient voided about 24 hours after the sulfathiazole therapy had been stopped. On the following day the hemolytic anemia was fully developed, and the blood at this time contained no sulfathiazole. The usual rapid excretion of sulfathiazole probably accounted for this. The fact that the first sign of the hemolytic anemia occurred 24 hours after the drug had been stopped may be explained as a delayed toxic reaction to the drug.

The laboratory findings pointing to acute hemolytic anemia were the red-colored urine which gave a strongly positive benzidine reaction and showed

few or no red blood cells, a positive urinary urobilinogen up to 1:125, erythrocytes which rapidly fell to 1,790,000 with 30 per cent hemoglobin, icterus index of 37.5, and a mean corpuscular thickness of 3.1 microns (normal range 1.7 to 2.5 microns). Laboratory evidence of toxic hepatitis as shown by impaired liver function was as follows: direct immediate van den Bergh which was transitory, hippuric acid synthesis in which less than one gram was excreted, bromsulphalein test showing as high as 85 per cent retention after 30 minutes, low blood cholesterol of 137.5 mg per cent, diminished total protein of 5.34 mg per cent with a 1:1 albumin-globulin ratio and no fibrinogen. Bile and urobilinogen were both present in the urine. There was the following laboratory evidence of renal damage: coarsely granular casts and renal parenchymal cells in the urine, and moderate azotemia, i.e., non-protein nitrogen 60 and urea nitrogen 40 mg per cent. Certain laboratory findings pointed to marked bone marrow activity with regeneration. These were a leukocytosis reaching 67,400, nucleated red cells totaling 4,400, blood platelets 590,000, reticulocytes 11.2 per cent, and a marked shift to the left, myelocytes and premyelocytes being present in the differential.

Whereas the hemolytic process was of relatively short duration and the hematopoietic recovery was reasonably prompt, as judged by laboratory findings, the renal and, especially, the hepatic damage persisted long beyond the time one would expect from the reports of similar cases in the literature.

DISCUSSION

In the reported cases of hemolytic anemia following sulfanilamide and sulfapyridine therapy, the association of syphilis with this complication has been pointed out. Syphilis is known to affect the hematopoietic system, as secondary anemia may develop in the secondary and tertiary stages of the disease. One must consider the possibility of syphilis causing some alteration of the blood possibly rendering the patient more susceptible to the development of acute hemolytic anemia, and at least two such fatal cases following sulfanilamide have been reported¹⁸. The serum of this patient gave persistently positive Wassermann and Kahn tests. The facts against this case being one of paroxysmal hemoglobinuria due to syphilis are that there was no previous history of hemoglobinuria when exposed to cold or at any time, that provocative tests when the patient's hands were kept in ice water were negative, and that the Donath-Landsteiner test was negative.

Another interesting feature of this case was the appearance of the acute hemolytic anemia after the first week of sulfathiazole therapy. In fact, it appeared at the end of the second week. Even if one were to take into account the few days that the drug was not given, the anemia began one day after the second course of treatment which lasted eight days. Acute hemolytic anemia following sulfanilamide and sulfapyridine administration has been shown to occur generally during the first to fifth days of treatment and, as a rule, not later than one week after the onset of therapy⁸. Here the anemia developed 15 days after the original administration of sulfathiazole and nine days after the beginning of the second course of therapy.

In 1938, Dameshek and Schwartz¹⁵ produced acute hemolytic anemias in experimental animals by the injection of heterophilic hemolytic serum. When

moderate doses were used, they were able to create acute hemolytic anemia with spherocytosis. This work has recently been confirmed¹⁴. Since spherocytosis is found largely in congenital hemolytic icterus, in which condition there is assumed to be a primary defect in the red cell, the report of other diseases or conditions in which spherocytosis is seen to occur would add to our present incomplete knowledge of this phenomenon. For these reasons spherocytosis was looked for and found in this case, and was corroborated by a mean corpuscular thickness which was above normal. The fragility test, however, was normal. In regard to this, it has been found that in atypical acquired hemolytic anemias there may be normal red cell fragility associated with spherocytosis and, also, increased fragility without spherocytosis. Further investigation would seem to be indicated along these lines in acquired hemolytic anemias due to sulfonamide therapy or other causes. It would be interesting to see if spherocytosis could be found in such cases and whether it would be associated with hemolysins in the blood. No hemolysins could be demonstrated in this case by the methods employed. Autoagglutination which frequently is seen in acute hemolytic anemia and in a variety of other conditions may or may not be associated with demonstrable hemolysins in the blood.

The marked leukocytosis with extreme shift to the left in this case might be termed a leukemoid reaction, although considerably higher leukocyte counts have been reported in reactions following sulfonamide therapy. Leukemoid reactions may occur alone and independently of other complications. They may be due to either of two other factors, acute hemolytic anemia or toxic hepatitis, which coexisted in this patient.

The jaundice in this case was due to the combination of acute hemolytic anemia and toxic hepatitis. The normal liver can excrete all the bilirubin brought to it and only the most extreme hemolysis will in itself produce jaundice¹⁰. A reason for this is that a hemolytic process of such a degree must inevitably lead to decreased excretory power of the liver from anoxemia alone. When jaundice results from excessive production of bilirubin, as in hemolytic anemia, there must be a simultaneous increase in the hepatic load and decrease in hepatic function, and definite, prolonged poor liver function was present in this case.

The pathogenesis of renal damage in the course of sulfonamide administration may be divided theoretically into three types: (1) renal damage resulting from direct toxic effect of the drug on the kidney parenchyma (that such a process occurs from therapeutic doses has not been proved¹⁷), (2) renal damage from the deposition of sulfonamide drugs or their derivatives in the kidney tubules, pelvis or ureters (This has been reported frequently with sulfapyridine and sulfathiazole^{3, 18}. The very slight microscopic hematuria and the absence of crystals in our case indicate that deposition of sulfathiazole or acetylsulfathiazole was probably not the basis of the renal damage), (3) renal damage from the deposition of hemoglobin or its derivatives in the tubules with blockage. This process which results from severe hemolysis as, for example, the reaction following transfusion of incompatible blood, was the most probable cause of the renal damage in the case presented. Ravid and Chesner,⁷ in their report of a fatal case of acute hemolytic anemia following sulfapyridine with autopsy, presented gross and microscopic corroboration of this process.

CONCLUSION

We have presented and discussed a case of acute hemolytic anemia, autoagglutination, leukemoid reaction, toxic hepatitis and renal damage following sulfathiazole therapy for a pneumococcus type VII lobar pneumonia in a man of 45, with recovery

BIBLIOGRAPHY

- 1 HARVEY, A M, and JANLWAY, C A The development of acute hemolytic anemia during the administration of sulfanilamide, *Jr Am Med Assoc*, 1937, cix, 12
- 2 LONG, P H, BLISS, E A, and FEINSTONE, W H Mode of action, clinical use and toxic manifestations of sulfanilamide further observations, *Jr Am Med Assoc*, 1939, cxii, 115
- 3 LONG, P H, HAVILAND, J W, EDWARDS, L B, and BLISS, E A The toxic manifestations of sulfanilamide and its derivatives, *Jr Am Med Assoc*, 1940, cxv, 364
- 4 BANNICK, E G, BROWN, A E, and FOSTER, F P The therapeutic effectiveness and toxicity of sulfanilamide, *Jr Am Med Assoc*, 1938, cxii, 770
- 5 ANTOPOL, W, APPENBAUM, I, and GOLDMAN, L Acute hemolytic anemia with autoagglutination following sulfanilamide therapy two cases, *Jr Am Med Assoc*, 1939, cxiii, 488
- 6 SPRING, M, and BERNSTEIN, I The coexistence of toxic hepatitis, acute hemolytic anemia and renal damage following sulfanilamide therapy, report of two cases, *ANN INT MED*, 1940, xiv, 153
- 7 RAVID, J M, and CHESNER, C Fatal case of (hemolytic) anemia and nephrotic uremia following sulfapyridine administration, *Am Jr Med Sci*, 1940, cxcix, 380
- 8 FOSBINDER, R I, and WALTER, L A Sulfanilamide derivatives of heterocyclic amines, *Jr Am Chem Soc*, 1939, lxi, 2032
- 9 LOTT, W A, and BERGEIM, F H 2(p-aminobenzenesulfonamide) thiazole, a new chemotherapeutic agent, *Jr Am Chem Soc*, 1939, lxi, 3593
- 10 VAN DYKE, H B, GREEP, R O, RAKE, G, and MCKEE, C M Observations on the pharmacology of sulfathiazole and sulfapyridine, *Proc Soc Exper Biol and Med*, 1939, xlii, 410
- 11 MCKEE, C M, RAKE, G, GREEP, R O, and VAN DYKE, H B Therapeutic effect of sulfathiazole and sulfapyridine, *Proc Soc Exper Biol and Med*, 1939, xlii, 417
- 12 SCHNITZER, M A Sulfanilamide and the negro (hemolytic anemia following therapy), *Ohio State Med Jr*, 1939, xxxv, 1204
- 13 KOLETSKY, S Fatal hemolytic anemia following administration of sulfanilamide, *Jr Am Med Assoc*, 1939, cxiii, 291
- 14 TIGERTT, W D, and DUNCAN, C N Erythrocyte morphology in experimental hemolytic anemia as induced by specific hemolysin, *Am Jr Med Sci*, 1940, cc, 173
- 15 DAMESHEK, W, and SCHWARTZ, S O Hemolysins as the cause of clinical and experimental hemolytic anemias, *Am Jr Med Sci*, 1938, cxlvi, 769
- 16 RICH, A Pathogenesis of forms of jaundice, *Bull Johns Hopkins Hosp*, 1930, xlvii, 338
- 17 MOLITOR, H, and ROBINSON, H Some pharmacological and toxicological properties of sulfanilamide and benzyl sulfanilamide, *Jr Pharm and Exper Therap*, 1939, xlv, 405
- 18 PEPPER, D S, and HORACK, H M Crystalline concretions in renal tubules following sulfathiazole therapy, *Am Jr Med Sci*, 1940, cxcix, 674
- 19 LONG, P H Thiazole derivatives of sulfanilamide, *Jr Am Med Assoc*, 1940, cxiv, 870
- 20 REINHOLD, J G, FLIPPEN, H F, and SCHWARTZ, L Toxicology of sulfathiazole in man, *Am Jr Med Sci*, 1940, cxcix, 393

- 21 FLIPPEN, H F, SCHWARTZ, L, and ROSE, S B Comparative effectiveness and toxicity of sulfathiazole and sulfapyridine in pneumococcic pneumonia, *ANN INT MED*, 1940, xiii, 2038
- 22 BLAKE, F G. The treatment of pneumococcal pneumonia, *New England Jr Med*, 1940, ccxxxiii, 661
- 23 CUTTS, M, BURGESS, A M, and CHAFFE, F. H The treatment of lobar pneumonia with sulfathiazole and sulfapyridine, *New England Jr Med*, 1940, ccxxxiii, 762

HYPERPARATHYROIDISM IN A PATIENT WITH ACROMEGALY *

By JULIUS CHASNOFF, M D, LOUIS FRIEDFELD, M D, and
ARTHUR M TUNICK, M D, *New York, N Y*

HYPERPARATHYROIDISM

THE parathyroids were first described as independent organs by Sandstrom ¹ in 1880, but their function remained in doubt until 1896 when it was demonstrated ² that their removal produced tetany. In 1909 MacCallum and Voegtlin ³ showed that the tetany of parathyroid insufficiency was associated with a fall in serum calcium and a rise in serum phosphorus.

In 1891, von Recklinghausen ⁴ described the anatomic syndrome of osteitis fibrosa cystica, distinguishing it from osteomalacia. Some years later, Eidheim ⁵ suggested that parathyroid enlargement found in association with osteitis fibrosa cystica was secondary to the bone changes. However, in 1926 Mandl ^{6, 7} found that parathyroid transplants were not affected by the bone changes in a patient with von Recklinghausen's disease, whereas the removal of a parathyroid tumor which was found in this patient was followed by clinical improvement. This suggested that the tumor was the underlying cause of the osseous changes. This relationship between von Recklinghausen's disease and the parathyroids was confirmed by Hannon and his co-workers ⁸ in 1926, Gold ⁹ in 1928, as well as Barr, Bulger and Dixon in 1929 ^{10, 11}. The latter group, along with Wilder ¹² and Snapper, ¹³ regarded hyperparathyroidism as a distinct clinical entity. Since then many reports have been published establishing the relationship of hyperparathyroidism to osteitis fibrosa cystica. Experimental evidence of the primary rôle played by the parathyroid hyperactivity has also been furnished by Jaffe, Bodansky and Blau ^{14, 15, 16}.

The observations of MacCallum and Voegtlin, ³ from which they concluded that the symptoms following parathyroidectomy were due to calcium deficiency, were confirmed and amplified by Luckhardt and Goldberg, ¹⁷ Salvesen, ¹⁸ and Collip ¹⁹. With the isolation of a potent parathyroid extract by Hanson ²⁰ and by Collip, ^{19, 21} and its administration in animals, disorders of calcium and phosphorus metabolism could be produced comparable to the picture in hyperparathyroidism ^{22, 23}.

* Received for publication April 19, 1941

From the Medical Services of Drs I W Held and A A Epstein, Beth Israel Hospital, New York City

Investigators agree that the chief rôle of the parathyroid hormone consists of its important influence upon the metabolism of calcium and phosphorus. The injection of parathyroid extract-Collip produced four cardinal effects²² (1) rise in serum calcium, (2) rise in urinary calcium excretion, (3) fall in serum phosphorus, and (4) rise in urinary phosphorus excretion.

Aside from the bone changes in von Recklinghausen's disease, other clinical and chemical alterations have been repeatedly noted. These were well summarized by Albright, Aub and Bauer²³. The clinical picture in its entirety presents features caused by (a) the hypercalcemia, such as weakness, lassitude, hypotonia and chronic constipation, (b) symptoms related to the skeletal system, such as bone pain and deformities, cysts of long bones and skull, spontaneous



FIG 1 Face shows prominent malar processes, overhanging supraorbital ridges, broad nose, thick lips and large ears

fractures, kyphosis and scoliosis, and (c) symptoms due to the transportation and excretion of calcium, such as polyuria, polydipsia, enuresis, nocturia, dysuria and renal calculi. There is also a constant increase in the plasma phosphatase in active cases of hyperparathyroidism²⁴.

ACROMEGALY

Our present knowledge of acromegaly dates back to 1886 when Pierre Marie,²⁵ in reporting two cases of this condition, suggested that it was a disease entity associated with the pituitary gland. He was the first to apply the name acromegaly to the clinical picture. However, Marie believed the condition to be the result of either hypofunction or dysfunction of the gland, and it remained for Minkowski²⁶ in 1887 to postulate hyperactivity of the pituitary as the responsible mechanism. This was verified by Benda²⁷ in 1900 when he found a constant relationship of eosinophilic adenomata with acromegaly. Cushing²⁸ then offered

experimental proof of the association of skeletal growth to the pituitary In 1929, Putnam and his associates²⁹ produced acromegaly in dogs by the injection of anterior lobe extracts

The clinical picture of acromegaly is well known The disease is characterized by the onset in early adult life of skeletal, cutaneous and visceral changes

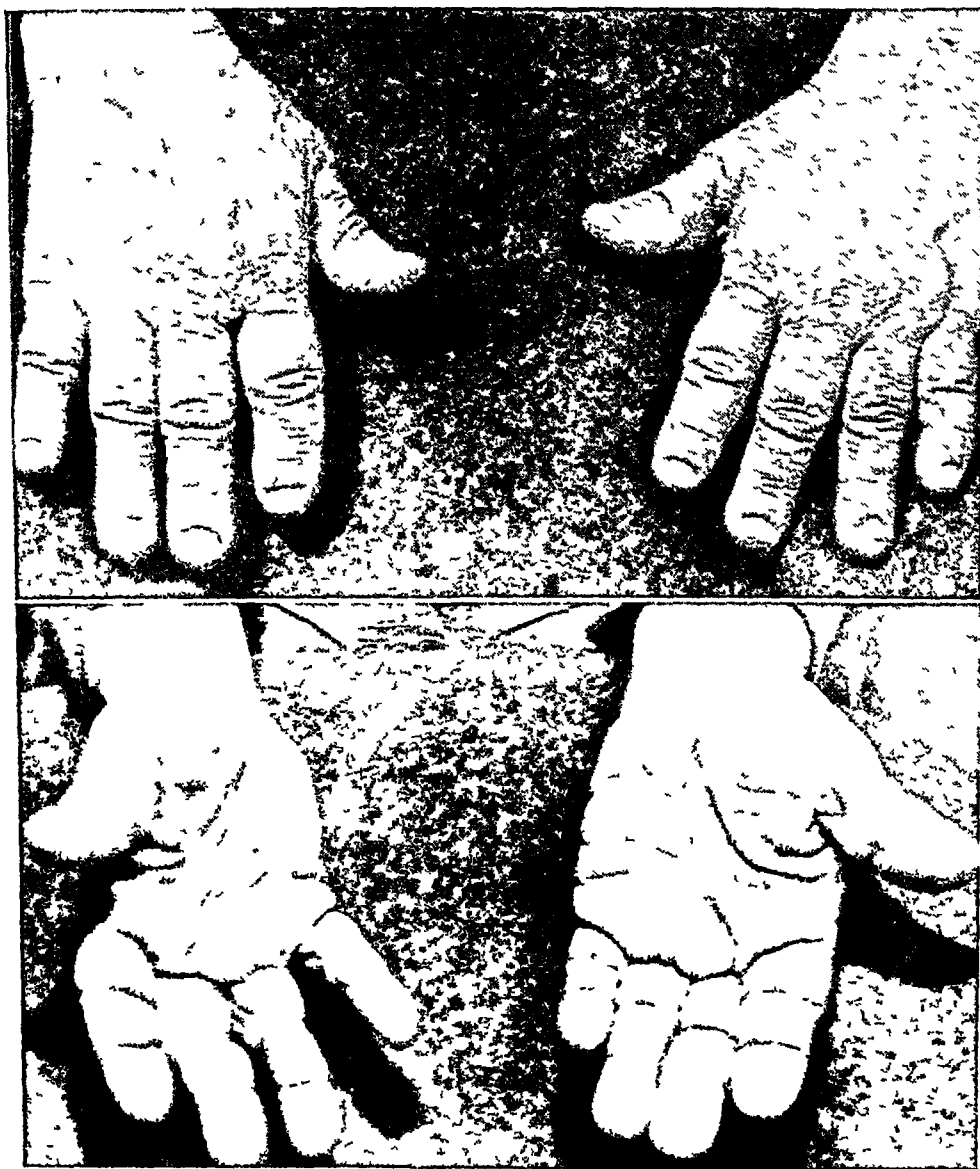


FIG 2 Hands show spading and loose, wrinkled, inelastic skin

There are increased dimensions of the hands and feet, broad palms and thick fingers producing a spade-like appearance, tufting of the tips of the distal phalanges, with hooking of the terminal phalanges of the thumbs, overgrowth of the bones of the face particularly involving the mandible, supraorbital ridges and nasal bones, enlarged frontal sinuses, massive protruding jaw (prognathism), widely spaced teeth, changes in the vertebrae resulting in kyphosis, wrinkled and thickened skin, hypertrichosis, gonadal hypertrophy with eventual atrophy and loss of libido splanchnomegaly, thick tongue, glycosuria and hyper-

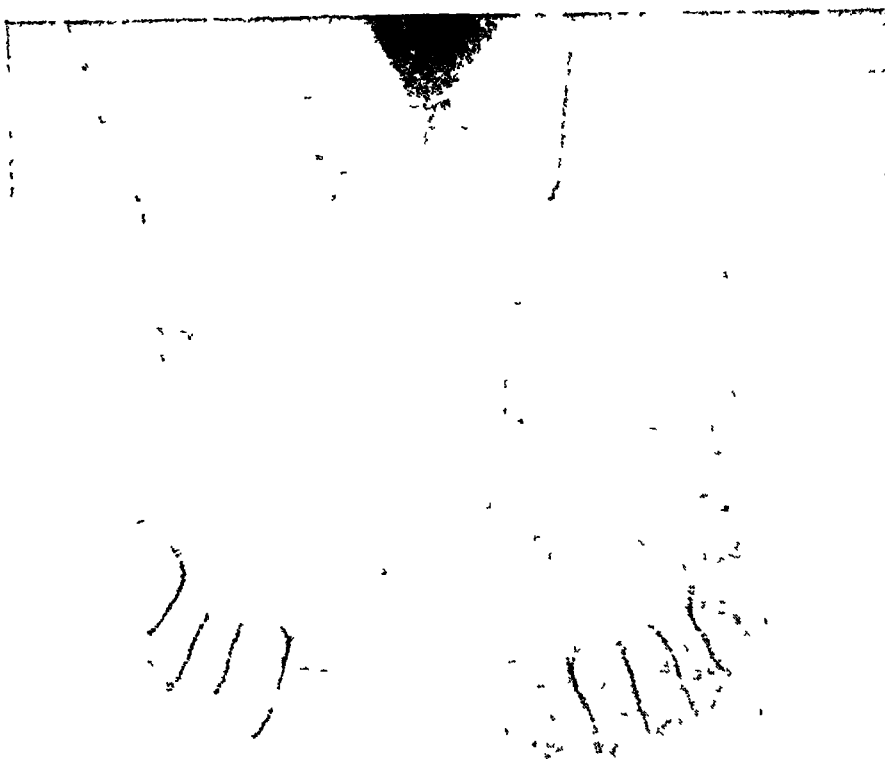


FIG 3 Spade feet

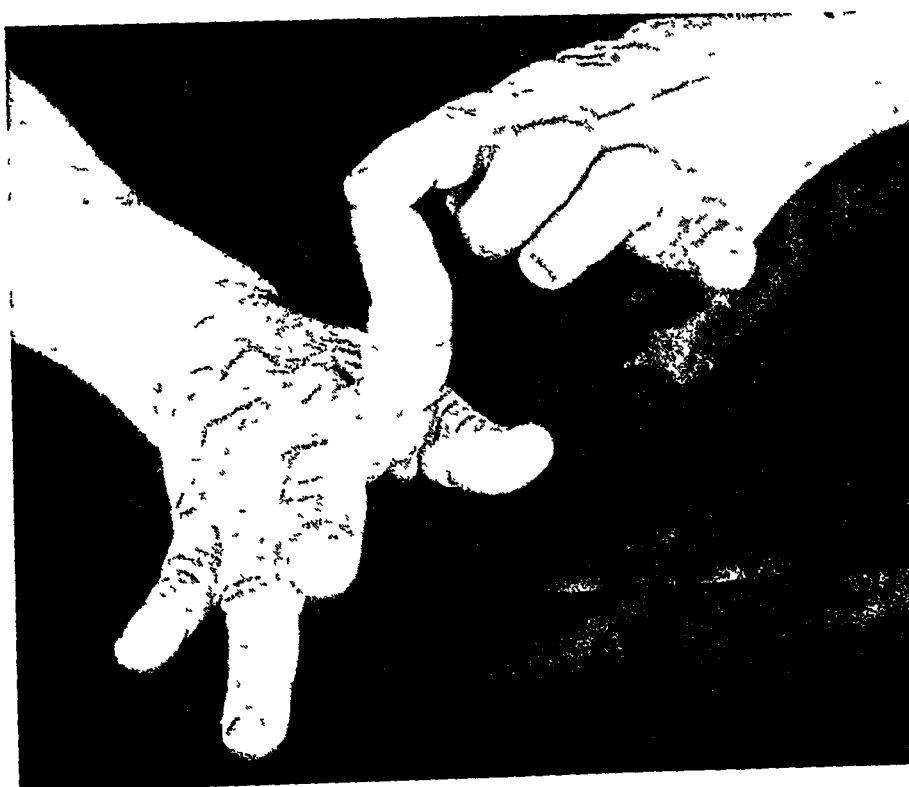


FIG 4 Demonstrating the marked hypotonia

glycemia The thyroid, thymus, parathyroids or adrenals may show hypertrophy or adenomatous growths

For the past several years we have been observing a patient who presents the clinical pictures of both hyperparathyroidism and acromegaly Because of the apparent rarity with which these conditions co-exist, we consider this case worthy of report In reviewing the literature we have encountered no similar instance This patient has added interest because she seems to suggest a probable relationship between the pituitary and the parathyroid glands



FIG 5 A large calculus fills the pelvis of the right kidney Several calculi are seen in the lower pole of the left kidney

CASE REPORT

On May 26, 1936, Mrs F D, aged 68 was admitted to the Beth Israel Hospital In 1924 she had had a radical mastectomy because of a lump in her right breast The remainder of her past history was irrelevant until 1928 when she was struck on the head by a heavy piece of baggage One month later she began to be troubled with severe parietal headaches At this time she became aware of the fact that her hands were becoming large and clumsy and her features coarse

It was not these changes in her appearance but recurrent urinary symptoms that were responsible for her hospitalization. Since 1928 she had been troubled with pain in the right lumbar region, occasionally radiating to the groin. In 1932 she was institutionalized elsewhere because of frank hematuria. Roentgen-rays taken at that time revealed right renal calculi. In 1935 there was a recurrence of the urinary bleeding along with left lumbar pain. Thereafter lumbar pain and hematuria recurred at frequent intervals. Three months prior to her admission to the Beth Israel Hospital roentgen-rays taken elsewhere showed bilateral renal calculi. For three years she had known that her blood pressure was high. For two years she had been troubled with obstinate constipation, weakness, headaches and occasional dizzy spells.



FIG 6 The pelvis shows extensive areas of osteoporosis involving the iliac bones and coarsening of the structure in the cancellated bone. The cortex of the right femur is markedly thickened and there are numerous small cyst formations in the head and the trochanter.

Physical examination showed a well preserved elderly woman with acromegalic features. She had prominent malar processes, overhanging supraorbital ridges, a broad nose, large lips and ears, and some prognathism (figure 1). There was slight concentric narrowing of the visual fields. The thyroid gland was not enlarged. Soft systolic murmurs were heard over the apex and aortic areas. The blood pressure was 160 mm Hg systolic and 96 mm diastolic. A mass was felt in the right flank. She had "spade" hands and wide feet (figures 2 and 3). There was diffuse pigmentation of the skin with some pigmented nodules on the face. A very striking feature was the marked hypotonia of the fingers (figure 4).

Laboratory studies showed urine which concentrated to 1020 with one plus albumin and many red and white cells. A sugar tolerance test showed a maintained high

level with 200 mg of glucose per 100 cc of blood after three hours. At two and three hours there were traces of sugar in the urine. The blood Wassermann test was negative. The blood non-protein nitrogen varied from 39 to 50 mg per cent. The blood count was normal. Repeated basal metabolic tests were within normal limits.

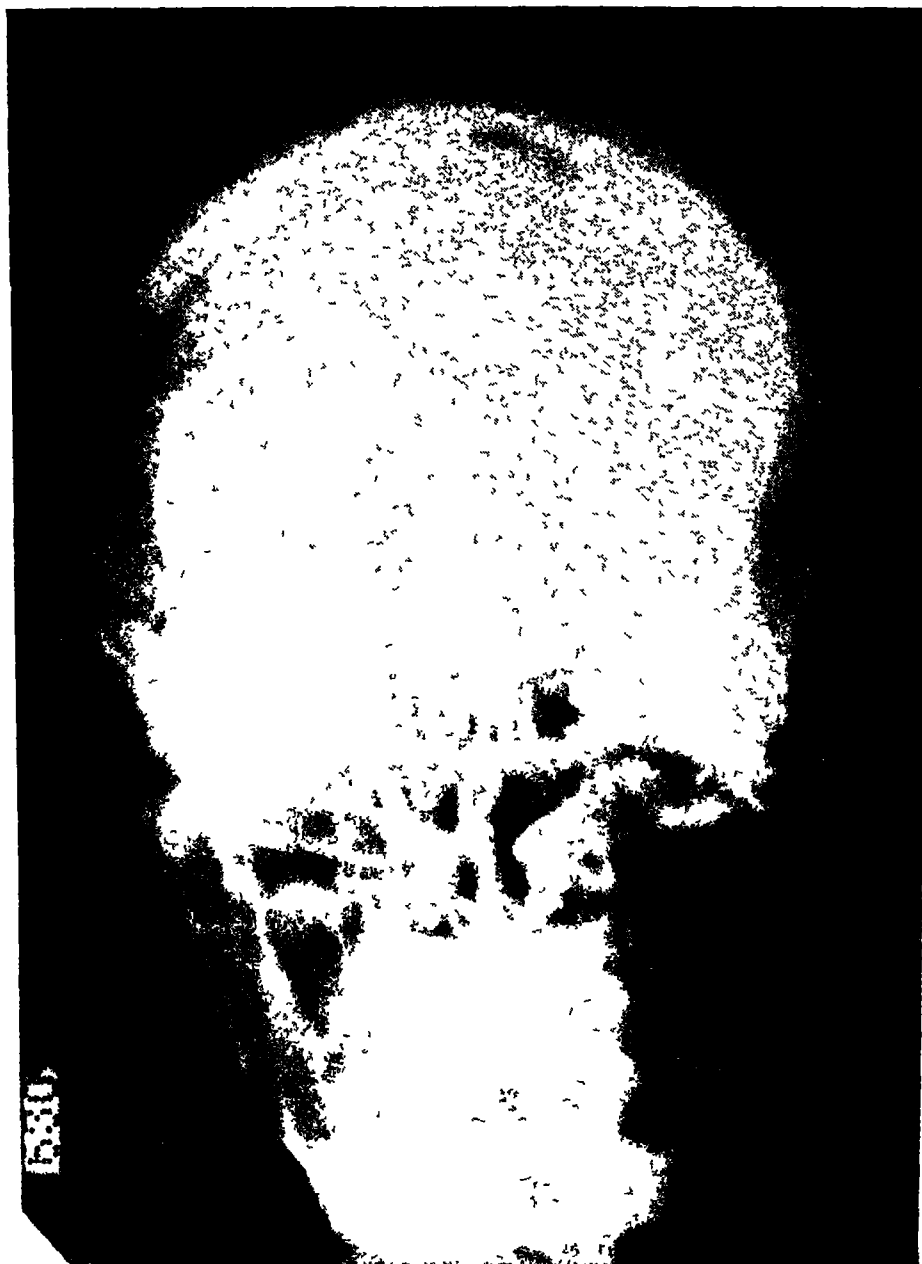


FIG 7 Roentgen-ray studies of the skull show diffuse osteoporotic changes and numerous areas of hyperostosis. The sinuses are enormously enlarged.

FIG 7 Roentgen-ray studies of the skull show diffuse osteoporotic changes and numerous the pelvis of the right kidney and calcareous deposits in the lower pole of the left kidney (figure 5).

Because of the renal calculi, marked hypotonia, constipation and weakness a clinical diagnosis of hyperparathyroidism was made. Further studies were undertaken in an effort to substantiate this impression.

Blood studies on three occasions showed an average serum calcium of 137 mg, and a serum phosphorus of 38 mg per 100 cc of blood. Plasma phosphatase was 84 Bodansky units, the normal for adults being 2 to 35 units. Efforts to determine her calcium balance were inconclusive.

The roentgen-ray studies of the skeletal system showed changes in the pelvic girdle, skull, long bones and vertebrae. The pelvis (figure 6) showed extensive areas of osteoporosis involving the iliac bones, in each of which large cyst-like areas were present. There was coarsening of the structure of the cancellated bone. The most



FIG 8 The lateral view of the skull shows marked widening of the diploetic layer which is occupied by coarse trabeculated bone. In the upper part of the frontal bone there is a large area of hyperostosis extending inward from the inner table. The vascular grooves are markedly deepened. The mastoid cells are enlarged. The sella turcica is markedly enlarged and the clinoids pneumatized.

pronounced changes were found in the skull (figures 7 and 8). Here diffuse osteoporotic changes and numerous areas of hyperostosis were present. The diploetic layer was markedly widened. In the upper part of the frontal bone there was a large area of hyperostosis extending inward from the inner table. The vascular grooves were deepened. The sinuses and mastoid cells were enormously enlarged. There was also marked enlargement of the sella turcica with pneumatization of the clinoids. All of the long bones showed extensive osteoporotic changes (figure 9). In addition, in several of them definite cyst formation could be demonstrated. These changes were marked in the right femur (figure 6) where there was also marked thickening of the cortex. The hands and feet (figures 10 and 11) showed characteristic tufting of

the terminal phalanges with hooking of the terminal phalanges of the thumbs. The widening of the phalangeal bases and slender shafts were particularly pronounced in the feet.

The hematuria gradually subsided and the patient was discharged after a seven week stay in the hospital. She was admitted a second time in July 1937 because of bleeding hemorrhoids and a severe anemia which necessitated two transfusions.



FIG 9 Roentgen-ray of the humerus shows osteoporotic changes and cyst formations similar to those seen in all the long bones. The ribs show diffuse lamellation and irregularity in outline due to disappearance of cortical bone and increase in cancellated tissue.

Her third admission, for recurring hematuria, occurred in June of 1938. Physical examination and renal findings were essentially the same as on her first admission. Blood studies now showed serum calcium of 11.8 mg, serum phosphorus of 3.5 mg, and plasma phosphatase 16.6 Bodansky units. Because the renal involvement was bilateral and the function of the right kidney impaired, surgical intervention was

deemed inadvisable. When the hematuria had subsided she was discharged. On her fourth admission, in August 1940, the chemical and roentgen-ray findings were essentially unchanged.

DISCUSSION

We have no way of knowing at present whether this patient has hyperplasia or adenoma of the parathyroid gland. Hyperparathyroidism is believed by many investigators to be a primary disturbance of the parathyroids. However, in this

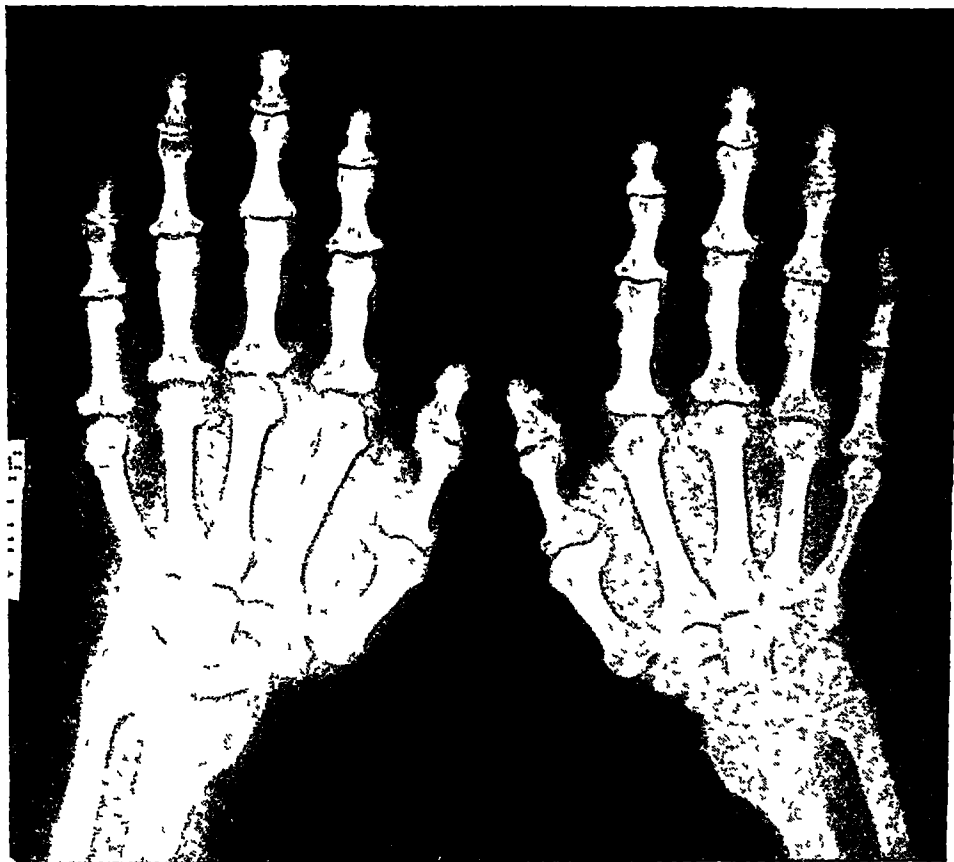


FIG 10 Roentgen-rays of the hands show marked thickening of the soft tissues so that the fingers are club-like in character. There is tufting of the terminal phalanges with hooking of the terminal phalanges of the thumbs.

case there arises the question of the relationship of the hyperparathyroidism to the acromegaly which apparently antedated it. Several possibilities may be suggested.

- 1 It is, of course, quite possible that we are here dealing with the coincidental existence of two distinct and unrelated disease entities.

- 2 Knowing that hyperplasia of many organs including endocrine glands may be found in patients with acromegaly, a fact which was demonstrated by Cushing and Davidoff,³⁰ the possibility of such hyperplasia resulting in clinical hyperfunction must be considered.

3 We must also bear in mind the frequency with which adenomata of the various endocrine glands exist in acromegaly. In fact, Davidoff³¹ refers to acromegaly as a syndrome with multiple adenomatosis.



FIG 11 Roentgen-rays of the feet show changes similar to those seen in the hands. The shafts of the phalanges are very slender and their bases markedly widened.

4 There is the possibility that a parathyrotropic substance elaborated in the pituitary may be responsible for the hyperparathyroidism. Hertz and Albright³² injected the urine of a patient with pituitary hyperplasia into rabbits, causing hyperplasia of their parathyroids. This suggested that a parathyrotropic substance was present, which could have originated only in the pituitary gland.

Whether the parathyroid hyperplasia or adenomata previously referred to are caused by such parathyrotropic substance or by the growth factor of the anterior lobe is not clear. Heitz and Kianes³³ have produced hypertrophy of the parathyroid cells by the injection of an extract of the anterior lobe of the pituitary. Hoffman and Anselmino³⁴ found histologic evidence of parathyroid hyperplasia following administration of pituitary extracts, although the total volume of the gland was not increased. In addition, they demonstrated an elevation of the serum calcium similar to that produced by parathormone administration.

Although Aschner³⁵ and Collip³⁶ found no changes in the parathyroids of hypophysectomized animals, Smith³⁷ reported definite atrophy. While the bulk of experimental work seems to point definitely to a pituitary influence on the activity of the parathyroid gland, there is no conclusive evidence of the existence of a parathyrotropic factor.¹⁰

CONCLUSIONS

A case of hyperparathyroidism in a patient with acromegaly is presented. The development of our knowledge of each of these conditions and its clinical picture are briefly reviewed. The possibilities of relationship of the von Recklinghausen syndrome to the acromegaly are considered.

BIBLIOGRAPHY

- 1 SANDSTRÖM, I. A new gland in the oesophagus, *Upsala lakaref. förh.*, 1880, xv, 441-471.
- 2 VISSALE, G., and GEFERRI, F. Results of parathyroidectomy, *Arch. ital. de biol.*, 1896, xxi, 459-464.
- 3 MACCALLUM, W. G., and VORSTLIN, C. On the relation of tetany to the parathyroid glands and to calcium metabolism, *Jr. Exper. Med.*, 1909, xi, 118-151.
- 4 VON RECKLINGHAUSEN, F. Fibrous or deforming osteitis, osteomalacia and osteoplastic carcinosis in their relationship to each other, *Festschr. Rudolf Virchow*, Berlin, 1891, 1-89.
- 5 ERDHEIM, J. Parathyroid findings in osteomalacia. *Sitzungsber. d. k. Akad. d. Wissensch., Math.-Naturw. Klasse*, 1907, cxvi, sect. 3, 311-370.
- 6 MANDL, F. Treatment of localized and generalized fibrous osteitis, *Wien klin. Wchnschr.*, 1926, lxxix, 1046-1048.
- 7 MANDL, F. Attempt to treat generalized fibrous osteitis by extirpation of parathyroid tumor, *Zentralbl. f. Chir.*, 1926, lxx, 260-264.
- 8 HANNON, R. R., SHORR, E., McCLELLAN, W. S., and DuBois, E. F. Case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of parathyroid bodies, metabolic study, *Jr. Clin. Invest.*, 1930, viii, 215-227.
- 9 GOLD, E. The significance of parathyroid enlargement in the generalized osteitis fibrosa of Recklinghausen. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1928, xh, 63-82.
- 10 BARR, D. P., BULGER, H. A., and DIXON, H. H. Hyperparathyroidism, *Jr. Am. Med. Assoc.*, 1929, xcii, 951-952.
- 11 BARR, D. P., and BULGER, H. A. Clinical syndrome of hyperparathyroidism, *Am. Jr. Med. Sci.*, cxix, 449-476.
- 12 WILDER, R. M. Hyperparathyroidism: tumor of parathyroid glands associated with osteitis fibrosa. *Endocrinology*, 1929, xiii, 231-244.
- 13 SNAPPFR, I. Tumor of accessory thyroid and bone deformities, *Nederl. tijdschr. v. geneesk.*, 1929, ii, 4758-4773.

- SNAPPER, I Parathyroid tumor and changes of bones, *Arch Int Med*, 1930, xlv, 506-523
- 14 JAFFE, H L, BODANSKY, A, and BLAIR, J E Fibrous osteodystrophy (osteitis fibrosa) in experimental hyperparathyroidism of guinea pigs, *Arch Path*, 1931, xi, 207-228
 - 15 BODANSKY, A, BLAIR, J E, and JAFFE, H L Experimental hyperparathyroidism in guinea pigs leading to osteitis fibrosa, *Jr Biol Chem*, 1930, lxxxviii, 629-647
 - 16 BODANSKY, A, and JAFFE, H L Parathormone dosage and serum calcium and phosphorus in experimental chronic hyperparathyroidism leading to osteitis fibrosa, *Jr Exper Med*, 1931, lmi, 591-604
 - 17 LUCKHARDT, A B, and GOLDBERG, B Preservation of the life of completely parathyroidectomized dogs by means of the oral administration of calcium lactate, *Jl Am Med Assoc*, 1923, lxxx, 79-80
 - 18 SALVESSEN, H A The function of the parathyroids, *Jr Biol Chem*, 1923, lvi, 443-456
 - 19 COLLIP, J B The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium, *Jr Biol Chem*, 1925, lxxiii, 395-438
 - 20 HANSON, A M The hydrochloric X of the bovine parathyroid and its phosphotungstic acid precipitate, *Mil Surgeon*, 1924, liv, 76-81
HANSON, A M Parathyroid preparations, *Mil Surgeon*, 1924, liv, 554-560
 - 21 COLLIP, J B, and CLARK, E P Further studies on the physiological action of a parathyroid hormone, *Jr Biol Chem*, 1925, lxxiv, 485-507
 - 22 LISSER, H, and SHILPARDSON, H C Parathyroids, function of parathyroid glandules, *The Cyclopedia of Medicine*, 1934, F A Davis Co, Philadelphia, ix, 656-685
 - 23 AUBRIGHT, F, AUB J C, and BAUER, W Hyperparathyroidism, common and polymorphic condition as illustrated by seventeen proved cases from one clinic, *Jr Am Med Assoc*, 1934, cii, 1276-1287
 - 24 KAY H D Plasma phosphatase enzyme in disease, particularly in bone disease, *Jr Biol Chem*, 1930, lxxxix, 249-266
 - 25 MARIE, P Two cases of acromegaly with especial hypertrophy of the upper and lower extremities and head, *Rev de méd Par*, 1886, vi, 297-333
 - 26 MINKOWSKI, O cited by WERNER, A A Endocrinology, clinical application and treatment 1937, Lea and Febiger, Philadelphia, p 102
 - 27 BENED, C Normal structure and several pathological changes of the human pituitary, *Arch f Anat u Physiol, Physiol Abt*, 1900, xlv, 373-380
 - 28 CUSHING, H Dyspituitarism Harver Lectures, 1910-1911, 31-45
 - 29 PUTNAM, T J, BENEDICT E B, and THER, H M Studies in acromegaly, experimental canine acromegaly produced by injection of anterior lobe pituitary extract, *Arch Surg*, 1929, xliii, 1708-1736
 - 30 CUSHING, H, and DAVIDOFF, L M The pathological findings in four autopsied cases of acromegaly with a discussion of their significance, *The Rockefeller Inst for Med Res*, N Y, 1927, monograph no 22
 - 31 DAVIDOFF, L M Hyperpituitarism and hypopituitarism *Bull New York Acad Med*, 1940, xvi, 227-243
 - 32 HERTZ, S, and AUBRIGHT, F The demonstration of a parathyreotropic substance in the urine of patients with hyperparathyroidism due to diffuse hyperplasia of all parathyroid glands, *Jr Clin Invest*, 1934, xiii, 698
 - 33 HERTZ, S, and KRANIS, A Parathyreotropic action of anterior pituitary histologic evidence in rabbit, *Endocrinology* 1934, xxiii 350-360
 - 34 HOFFMAN, F and ANSELMINO K J The effect of anterior pituitary extracts on blood calcium level *Klin Wchnschr* 1934, xiii, 44-45
 - 35 ASCHOFF, B The function of the pituitary, *Arch f d ges Physiol*, 1912, cxlvi 1-146

- 36 COLLIP, J B Diabetogenic, thyrotropic adrenotropic and parathyrotropic factors of pituitary, Jr Am Med Assoc, 1935, cxi, 916-921
- 37 SMITH, P E Disabilities caused by hypophysectomy and their repair, tuberal (hypothalamic) syndrome in rat, Jr Am Med Assoc, 1927, lxxviii, 158-161
- 38 GREENWALD, I, and GROSS, J Effect of long continued administration of parathyroid extract upon excretion of phosphorus and calcium, Jr Biol Chem, 1926, lxxviii, 325-333
- 39 ALBRIGHT, F, and ELLSWORTH, R Studies on physiology of parathyroid glands, calcium and phosphorus studies on case of idiopathic hypoparathyroidism, Jr Clin Invest, 1929, vii, 183-201
- 40 COLLIP, J B Corticotropic (adrenotropic), thyrotropic and parathyrotropic factors, Jr Am Med Assoc, 1940, cxv, 2073-2079

EDITORIAL

HYPERCALCEMIA AND RENAL INJURY

It is well known that with skeletal immobilization there occurs bone demineralization. It is also well known that a considerable portion of the lime salts exported from the body in this process are handled by the kidneys. The excess excretion of calcium in the urine, or hypercalciuria, is presumably the reason for the frequency of urinary tract stones in patients with healing fractures, an association which has been observed for many years.

That hypercalcemia can be a direct result of the rapid mobilization of lime salts during the development of atrophy of disuse has only very recently been suggested. Two years ago, following an attack of poliomyelitis, a young patient of Dr. William Orr's, in Buffalo, developed renal insufficiency, and, associated with the usual chemical findings in the serum of uremia, there was repeatedly observed a high serum calcium.¹ It was independently suggested by Dr. Fuller Albright of Boston and Dr. E. A. Park of Baltimore that the hypercalcemia might be due to the rapid mobilization of lime salts from disuse atrophy, and that the hypercalcemia per se might have caused damage to the renal tubules with resulting uremia.

Orr followed up this lead and examined the serum calcium in 11 cases of poliomyelitis in the paralytic stage, finding hypercalcemia in 10 of them.¹ Wilkins² also found serum calcium elevations in some of the paralytic cases he examined at the Children's Hospital School with this point in mind.

With this background workers were on the alert for a syndrome of renal damage in association with extensive skeletal immobilization. Last spring Albright and his colleagues at the Massachusetts General Hospital reported³ the case of a 14-year-old boy who, while in an extensive body cast for a fractured femur, developed signs and symptoms of severe renal damage. Hypercalcemia, hypercalciuria, albuminuria, inability to concentrate the urine and many calcium phosphate casts were found. With skeletal mobilization the clinical picture began to improve rapidly, and at discharge the kidney function tests were normal. The interpretation of the sequence of events in this case by the authors was that more calcium was presented to the kidneys than could be handled, and hypercalcemia resulted, the hypercalcemia injured the renal tubules. When, by skeletal mobilization, the outflow of lime salts from the bones was allayed, the situation soon righted itself and no permanent residual kidney injury was found to have resulted.

That hypercalcemia can of itself cause renal injury seems altogether likely. Other conditions commonly associated with hypercalcemia are hy-

¹ ORR, W. J. Personal communication—to be published.

² WILKINS, L. Personal communication.

³ ALBRIGHT, F., BURNETT, C. H., COPE, O. and PARSONS, W. Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism, *J. Clin. Endocrinology*, 1941, 1, 711.

parathyroidism and over-vigorous therapy with products of irradiated ergosterol, and in both of these renal damage is very common. Hypercalcemia occurs sometimes, of course, in extensive destructive bone diseases such as carcinomatosis and multiple myeloma.

We wish to point out and emphasize here that, with bone atrophy of disuse *hypercalcemia and renal damage can occur*. That there must be factors operating other than atrophy of disuse alone seems obvious, for otherwise everyone with fractures warranting extensive skeletal immobilization would develop uremia. What these other factors may be remains unknown for the present. We may postulate, however, that certain factors would tend to make more likely the development of the syndrome, for example:

(1) A rapidly growing bone which, in a child, is supposed also to atrophy more rapidly. Hence we would expect to find the syndrome more common among children than among adults.

(2) Mobilization of lime salts from the strong dense bones of a day laborer would present the kidney with more work than if the immobilized patient were a sedentary worker or one who, for some other reason, already had rarefied bones.

(3) Anything which would tend to raise the serum calcium, such as the administration of large amounts of calcium, especially if vitamin D were given in addition. There is some reason to believe that vitamin D may be a much more vigorous agent in elevating the serum calcium when the patient is in bed than when he is up and about. Butler⁴ has made an interesting observation in patients with resistant rickets. These patients require 300,000 to 1,000,000 I U calciferol per day in the ambulatory state to remain free of evidences of rickets and to keep the serum calcium and phosphorus levels normal. When such a patient is brought into the hospital and immobilized, this same dose of calciferol proves far too high and hypercalcemia rapidly ensues. The administration of "high milk diets and vitamin D" is a very common practice on fracture services, and one wonders if the use of these measures had not best be much more closely supervised.

(4) The use of alkalis can, under certain circumstances, produce calcification of renal tubules. The production of an alkaline urine would also tend to make more likely the precipitation of calcium phosphate and hence the production of urinary lithiasis.

(5) Certain types of renal injury, such as would reduce the ability to excrete calcium, would tend to cause or increase the hypercalcemia. As a matter of fact, the renal tubular injury caused by the hypercalcemia may reduce the functional ability to excrete calcium, and thus a vicious circle would be set up. Much more knowledge in regard to exact localization of renal tubular function will have to be available before we can speculate further along these lines.

⁴ BUTLER, A. M. Personal communication—to be published.

(6) An inadequate output of water would tend to precipitate the lime salts in the urine by increasing their concentration. It would also tend to act in the direction of lessened excretion by the kidneys and hence would favor hypercalcemia. It would seem wise, therefore, to force fluids to the point of insuring an adequate output of urine in cases with much skeletal immobilization.

Although a considerable portion of the above discussion is based on indirect evidence, the observation that sufficient renal damage may occur in association with states of skeletal rarefaction as to produce severe renal damage is of the greatest importance. Further work of a fundamental nature on the subject seems definitely indicated. Certain hitherto unidentified toxic states may be found to be due to hypercalcemia, and the frequent occurrence of uremia in elderly patients with fractures may be due, in some instances, to such a mechanism.

J E H

REVIEWS

Practical Bedside Diagnosis and Treatment By HENRY JOACHIM, M D, F A C P
828 pages, 26 × 16.5 cm Charles C Thomas, Springfield, Illinois 1940 Price,
\$7.50

In his preface to this volume the author states that it is largely a presentation of his own experiences during 35 years of practice and teaching, emphasizing bedside diagnosis and treatment. This personal touch is noticeable throughout the book, as it is written informally, in an almost conversational style.

There is, however, nothing in the plan of presentation of the subject matter that could facilitate differential diagnosis. The grouping of diseases is identical with that used in most standard textbooks of medicine. Some important diseases are omitted or neglected. For example, Rocky Mountain spotted fever is given only two lines, whereas many less important infections are described in detail.

In some cases, the recommended treatment leaves something to be desired, notably the description of the serum therapy of pneumonia.

In general, "Practical Bedside Diagnosis and Treatment" is a sound enough textbook, but is probably not up to the standards of other texts readily available to the student and practitioner.

T N C

The Premature Infant, Its Medical and Nursing Care By JULIUS H. HESS, M D,
and EVELYN C. LUNDEEN, R N 309 pages, 21 × 14 cm J. B. Lippincott Co.,
Philadelphia 1941 Price, \$3.50

"The Premature Infant," a very excellent and authoritative work, is divided into 28 chapters. The first few chapters discuss the classification of prematures, their etiology, physiologic development, and growth. Approximately the next 150 pages are devoted to nursing routines, nursery requirements, feedings, transportation, etc. Clinical conditions, such as cyanosis, hemorrhage, respiratory diseases, anemia, syphilis, etc., are discussed in the last 10 chapters.

Emphasis is especially placed on nursing care and nursery requirements. This is done in a very unified and detailed manner. Home care for the premature is also explained. The clinical subjects are not discussed in great detail, but only as these conditions affect the premature.

W M S

Diseases of the Thyroid Gland By ARTHUR E. HERTZLER, M D 670 pages,
26 × 19 cm Paul B. Hoeber, Inc. New York City 1941 Price, \$8.50

Dr. Hertzler, best known to the American public as the author of "The Horse and Buggy Doctor," states that this book is "in no wise a treatise on diseases of the thyroid gland, but a record of his studies extending over a period of nearly fifty years." This statement explains the almost complete absence of discussion of the work of other investigators, and the scarcity of references to the medical literature, of which only six are given in the entire book. Of the six articles referred to four are written by members of Dr. Hertzler's clinic. Several chapters are written by associates.

The author's personality and opinions dominate the material presented. A vivid method of writing, exemplified in Dr. Hertzler's autobiography, has been used in the present work. Occasionally the style serves to hold the reader's interest but more often the anecdotes and pungent comments lead to confusion and interruption of one's train of thought.

It is unfortunate that practically no statistical analysis of Dr. Hertzler's great mass of material is presented, except in the chapter on hepatic insufficiency by C. R.

Schmidt This is especially disappointing when one considers that the author devotes a great deal of space to his attempt to prove that total thyroidectomy in the adult is never followed by myxedema, and that myxedema associated with a palpable thyroid can be cured by the removal of the gland Statistics might also reinforce the author's opinions on cardiotoxic goiter, as described in chapter seven

Dr Hertzler has drawn liberally on his great store of pathologic material The book is profusely illustrated, chiefly by photographs of gross and microscopic sections of glands removed at operation The chapter on thyroiditis, describing suppurative and nonsuppurative thyroiditis, Hashimoto's and Riedell's strumas, is one of the best

Except for a slip on page 515, the Publisher bears out his reputation as a maker of beautiful medical books

T N C

The Minds and Nerves of Soldiers By EDWARD L HANFS, M D 221 pages, 23.5 × 16 cm The Logan Press, Pasadena, California 1941 Price, \$3.00

This is essentially an autobiography in which the author sets forth his experiences while serving as a neuropsychiatrist with the A E F during the First World War The material is not very well integrated or organized, and the attempt to coordinate past experiences with the vital needs of the present is weak One-third of the book consists of case records covering a wide range of neuropsychiatric disabilities in which the author presents his clinical experiences and this is mostly descriptive in fashion The remainder is devoted to the author's personal experiences, his impressions and his philosophy as it is related to military psychiatry

Possibly the book is of some value to the beginner in this specialty but it has little to offer the trained neuropsychiatrist aside from its historical interest From it, one is impressed by a need in the armed forces of a sufficient number of psychiatrists not only to detect and eliminate potential mental disabilities but also to provide adequate care and treatment of essentially a personal, highly individualized nature

H W N

Emotions and Bodily Changes A Survey of Literature on Psychosomatic Interrelationships, 1910-1933 Second Edition By H FLANDERS DUNBAR, M D, Med Sc D, Ph D 601 pages, 24 × 16 cm Columbia University Press, New York City 1938 Price, \$5.00

Medical men have always recognized and been curious about the fact that mental states do influence bodily processes and are influenced by them in turn This curiosity regarding the influence of "mind over body" has only recently taken the form of serious scientific research The phrase "psychosomatic medicine" has been coined to express this new interest Psychiatrists have long taught us that it is futile to think of diseases as being caused either by organic or psychogenic factors The organism as a whole (mind and body) is involved in every pathologic process, whether attention is focused on etiology, course or treatment

Dr Dunbar has been a pioneer in psychosomatic medicine, in studying scientifically this baffling problem Her book, *Emotions and Bodily Changes*, must be referred to by anyone who wants to study or contribute to this field Although this field is comparatively new, much ground work was done during the period 1910 to 1933 Incidentally, the present edition surveys much of the literature which appeared since the first edition (1935)

This book is primarily intended for reference and has excellent subject and author indices But in spite of the fact that 2358 articles are quoted from or referred to, it is logically arranged and presented in very readable form Especially valuable to read are the first chapters, dealing with the problems studied and the methods for studying them, and the final chapter on therapeutic considerations Certainly no medical library is complete if it does not have this book, in its latest edition, for reference

H W N

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members

Books

- Dr Jerome E. Andes, F A C P, Tucson, Ariz — "Synopsis of Applied Pathological Chemistry",
Dr Hugh R. Butt, F A C P and Dr Albert M. Snell, F A C P, Rochester, Minn — "Vitamin K",
Dr Reginald Fitz, F A C P, Boston, Mass — "The Surprising Career of Peter La Terrière, Bachelor in Medicine",
Dr John A. Kolmer, F A C P, Bala-Cynwyd, Pa — "Approved Laboratory Technique" and "Clinical Immunology, Biotherapy and Chemotherapy",
Dr James Ralph Scott, F A C P, New York, N Y — "Diabetes",
Joseph F. Siler, F A C P, Col., (MC), U S Army, Retired — "Immunization to Typhoid Fever",
Dr Gerald B. Webb, F A C P, Colorado Springs, Colo — "Tuberculosis",
Dr John B. Youmans, F A C P, Nashville, Tenn — "Essentials of the Diagnostic Examination"

Reprints

- Dr Marcus Backer, F A C P, Bridgeport, Conn — 1 reprint,
Dr N. Judson Bender (Associate), Shreveport, La — 1 reprint,
Dr J. Edward Berk (Associate), Philadelphia, Pa — 4 reprints,
Dr Nathan Blumberg, F A C P, Philadelphia, Pa — 1 reprint,
Dr Grafton Tyler Brown, F A C P, Washington, D C — 1 reprint,
Dr Anthony V. Cadden, F A C P, Wauwatosa, Wis — 2 reprints,
Dr Verne S. Caviness, F A C P, Raleigh, N C — 2 reprints,
Dr Fred M. Drennan, F A C P, Chicago, Ill — 1 reprint,
Dr Reginald C. Edson (Associate), Hopemont, W Va — 1 reprint,
Dr William Freeman, F A C P, Worcester, Mass — 1 reprint,
Dr Charles F. Gormly, F A C P, Providence, R I — 3 reprints,
Dr Elmer Haynes (Associate), Madison, Wis — 2 reprints,
Dr Lyman H. Hoyt, F A C P, Boston, Mass — 2 reprints,
Dr Edward Kupka, F A C P, Los Angeles, Calif — 2 reprints,
Oza J. LaBarge, F A C P, Lieut., (MRC), U S Army — 1 reprint,
Dr Michael Lake, F A C P, New York, N Y — 1 reprint,
Dr David O. N. Lindberg, F A C P, San Diego, Calif — 1 reprint,
Dr Philip H. Livingston, F A C P, Chattanooga, Tenn — 1 reprint,
Dr David Salkin, F A C P, Hopemont, W Va — 2 reprints,
Dr David J. Sandweiss, F A C P, Detroit, Mich — 5 reprints,
Dr Philipp J. R. Schmahl, F A C P, New York, N Y — 1 reprint,
Dr James Ralph Scott, F A C P, New York, N Y — 3 reprints,
Dr Christopher C. Shaw, F A C P, Warrington, Fla — 1 reprint,
Dr Albert Soiland, F A C P, Los Angeles, Calif — 2 reprints,
Dr Frederick G. Speidel, F A C P, Louisville, Ky — 1 reprint

REGIONAL MEETING OF ILLINOIS MEMBERS

The first Regional Meeting of Fellows and Associates in the northern district of Illinois was held at Chicago, December 6, 1941, but the meeting was expanded to include the entire state. Dr. LeRoy H. Sloan, Chicago, Governor for Northern Illinois, and Dr. Cecil M. Jack, Decatur, Governor for Southern Illinois, conducted the meeting in collaboration, and College members from near-by points in the adjoining states of Wisconsin, Indiana, and Michigan were also invited.

Dr. George H. Coleman, Chicago, was Chairman of the Committee on Arrangements, and Dr. Willard O. Thompson, Chicago, was Chairman of the Program Committee. The program, starting at 9:00 a.m., was as follows:

Morning Session

Governor Cecil M. Jack, *Presiding*

- 9:00 "Treatment of Experimental Renal Hypertension with Renin" G. E. Wakerlin and C. A. Johnson, Chicago
- 9:10 "Carcinoma of the Pancreas: A Clinical and Pathological Study of 75 Cases" Aaron Arkin and S. W. Weisberg, Chicago
- 9:20 "Thiamin in Perspiration" Leo Hardt and Eugene U. Still, Ph.D., Chicago
- 9:30 "Improved Methods of Diagnosis of Protozoan Infections of the Intestine" Alva A. Knight, Chicago
- 9:40 "Diagnostic Problems in Coronary Thrombosis" E. W. Cannady, East St. Louis

Intermission (10 minutes)

- 10:00 "Effects of Various Mixtures of Insulin and Protamine Zinc Insulin" Arthur R. Colwell, Evanston
- 10:10 "Chronic Combined Acetanilid and Amidopyridine Poisoning: A Case Report" V. Thomas Austin, Urbana
- 10:20 "Pneumonia in an Army Station Hospital in 1941" Emmet H. Pearson, Fort Sheridan
- 10:45 to 12:00 Clinico-pathologic Conference Conducted by James P. Simonds, Professor of Pathology, Northwestern University Medical School. *Clinicians*: Ralph C. Brown, James G. Carr, Joseph A. Capps

Luncheon

- 12:00-1:00 p.m. Luncheon in the Dining Room of New Wesley Memorial Hospital. Written questions on the morning program were submitted and answered at a round table discussion during Luncheon with Governor LeRoy H. Sloan, presiding.
- 1:00-2:00 p.m. Inspection of Hospital. Drs. Raymond McNealy and Gilbert Marquardt.

Afternoon Session

- 2:00-3:30 Medical Progress in Review. Willard O. Thompson, presiding. (Each presentation limited to 5 minutes.)

"Diabetes"	Robert W. Keeton
"Diseases of the Liver"	Sidney A. Portis
"Chemotherapy"	Paul Rhoads
"Pneumonia"	Italo F. Volini
"Contagious Diseases"	Archibald A. Hoyne
"Surgical Shock"	Warren Cole
"Physiology"	Andrew C. Ivy
"Hypertension"	M. Herbert Barker

Vitamins "	Clifford Barborka
"Endocrinology "	Willard O. Thompson
"Arthritis "	Ernest E. Irons
"Cardiology "	Gilbert Marquardt
"Pancreatic Hormones "	Lester R. Dragstedt
"Peptic Ulcer "	Walter L. Palmer

— — —

Vice-President Samuel E. Munson, *Presiding*

- 3 30 "Irradiation of the Pituitary and Adrenals for Essential Hypertension " James H. Hutton, Chicago
- 3 40 "Mechanism of Death from Mercurial Diuretics" Howard Lindberg, Maurice Thomas and M. Herbert Barker, Chicago
- 3 50 "Rôle of Emotions in Medicine " F. J. Braceland, Chicago
- 4 00 "Rôle of Stimulants in the Treatment of Barbiturate Poisoning " Richard Kohn Richards, North Chicago
- 4 10 "Present Status of Stilbestrol " S. G. Taylor, III and W. O. Thompson, Chicago
- 4 20 "Specific Precipitin Antisera for Tissue Proteins" William H. Welke, Chicago
- 4 30 "Medical Preparedness " Major Harold Lueth, Chicago

There were a number of subjects for general discussion which, due to lack of time, were read by title.

The evening program was held at the Knickerbocker Hotel, consisting of a social hour followed by dinner, after which Dr. Edward L. Bortz, F. A. C. P., Philadelphia, presented an address on "Medical Progress and the American College of Physicians." Short talks were made by distinguished guests, and Dr. George Coleman presided as Toastmaster.

Approximately 150 members were in attendance. This meeting was the first medical scientific meeting to be held in the New Wesley Memorial Hospital on the Campus of Northwestern University.

— — —

REGIONAL MEETING OF MARYLAND MEMBERS

The fall meeting of the Maryland Chapter of the American College of Physicians was held at a dinner at the Belvedere Hotel on Thursday December 18, 1941. There were 67 present including guests, Dr. Thomas Rivers, Director of the Rockefeller Institute, Mr. E. R. Loveland, Executive Secretary of the College, and the resident physicians of a number of the Baltimore hospitals. Dr. John King, President of the Maryland Chapter, presided. Dr. King introduced Mr. Loveland who brought greetings from Dr. Roger Lee, President of the College. Mr. Loveland spoke of the growth of the College, the work of the College in Defense, and concluded with the advice that we should "protect our American Institutions and our College."

Dr. King next introduced Dr. Thomas Rivers who gave a very stimulating talk on the physical, chemical and biological characteristics of vaccine virus — LEWIS P. GUNDRY, M. D., F. A. C. P., *Secretary*

On December 10, 1941, Dr. Rufus S. Reeves, F. A. C. P., Philadelphia, Pa., spoke on "The Rôle of the Physician in Local Disasters" at a meeting on National Defense of the Philadelphia County Medical Society.

Dr. Herbert T. Kelly, F. A. C. P., Philadelphia, Pa., presented a paper on "The Nutrition Needs of Our Community" as part of The Forum at The Nutrition Institute of Philadelphia, November 8, 1941.

Dr Kelly also presented a paper on "Nutrition as It Applies to the General Diseases" and a film in natural color, "The Modern Science of Nutrition and Nutritional Deficiency Disease," before the Cambria County Medical Society at Johnstown, Pa, November 13, 1941

John W Shuman, Sr, F A C P, Lt Col, (MRC), U S Army, has been elected an honorary member of the Hollywood Academy of Medicine

On July 21, 1941, George C Turnbull (Associate), Captain (MRC), U S Army, was appointed Chief of the Medical Service at the Station Hospital, Fort Bliss, Tex

Dr James H Hutton, F A C P, and Dr Robert S Berghoff, F A C P, both of Chicago, Ill, have been appointed members of the Board of Advisers in the Department of Public Health for the State of Illinois, by Governor Dwight H Green

Dr Bernard E McGovern, F A C P, San Fernando, Calif, has been appointed Medical Director of Hillcrest Sanatorium, La Crescenta, Calif Dr McGovern has also become a member of the Tuberculosis Division of the Los Angeles City Health Department

Dr John M Nicklas, F A C P, Trudeau, N Y, has recently been appointed a member of the Committee on Sanatorium Standards of the American Trudeau Society Dr. Harold G Trimble, F A C P, Oakland, Calif, is President and Dr Henry C Sweany, F A C P, Chicago, Ill, is President-Elect of this Society

Dr Hyman I Goldstein (Associate), Camden, N J, addressed the Fall Clinical Conference of The Medical Society of New Jersey on December 3, 1941, at Elizabeth, N J, on "Ulcer and Cancer of the Stomach in the Middle Ages"

The Alpha Nu Chapter of Phi Rho Sigma, located at the University of Texas Medical School, had inauguration of the Phi Rho Sigma Lectureship for the purpose of bringing before the students of this School eminent physicians This lectureship has been established in honor of the deceased alumni of the chapter, many of whom have been prominent members of the Faculty of the University of Texas Medical School The first lectures were given December 1, 1941 by Dr R E Dyer on "Typhus Fever" and by Dr. R L Cecil, F A C P, on "Rheumatoid Arthritis"

The Omaha Mid-West Clinical Society held its 9th Annual Assembly in Omaha, Nebr, October 27-31, 1941 Among the guest speakers at this meeting were

Dr W Osler Abbott, F A C P, Philadelphia, Pa — "Nonsurgical Treatment of Obstruction of the Bowel," "The Action of Drugs on the Alimentary Tract" and "Functional Disorders of Digestion (Clinic)";

Dr Byrl R Kirklin, F A C P, Rochester Minn — "The Early Manifestations of Gastrointestinal Cancer" and "Evaluation of Roentgenologic Methods in the Diagnosis of Diseases of the Gall-Bladder and Duodenum",

Dr Albert M Snell, F A C P, Rochester, Minn — "Recent Advances in Vitamin Therapy," "Supposedly Rare Conditions Producing Abdominal Pain" and "Diseases of the Liver and Bile Passages (Clinic)",

Dr. S Bernard Wortis, F A C P, New York, N Y — "Injury to the Brain and Spinal Cord," "Brain Metabolism and Neuropsychiatric Disorders" and "Brain Tumors (Clinic)"

The College members in Omaha who participated in this program were
 Dr A David Cloyd, F A C P—"The Mechanism, Recognition and Management of Congestive Heart Failure",
 Dr F Lowell Dunn, F A C P—"The Visualization of Normal and Pathologic Chest Sounds by the Use of the Cathode Ray Tube",
 Dr Eslev J Kirk, F A C P—"Clinical Interpretation of the Various Laboratory Procedures of Hypertension and Nephritis",
 Dr George P Pratt, F A C P—"The Incidence, Differential Diagnosis and Treatment of Bacillary Dysentery",
 Dr Chester Q Thompson, F A C P—"Transfusions of Blood and Plasma",
 Dr Raymond L Traynor, F A C P—"Clinical Manifestations of Vitamin B Deficiency",
 Dr Albert F Tyler, F A C P—"Newer Radiographic Methods in Gastrointestinal Diagnosis",
 Dr Harrison A Wigton, F A C P—"Hysteria and Personality",
 Dr J Harry Murphy (Associate)—"The Early Recognition and Immediate Treatment of Cerebral Hemorrhage in the Newborn",
 Dr John C Sharpe (Associate)—"Rheumatic Heart Disease"
 Among the scientific exhibits the exhibit of Dr F Lowell Dunn, F A C P won the Premier Award for "Originality and excellence of individual investigation," and the exhibit of Dr J Harry Murphy, Assoc, won an honorable mention for "Excellence of presentation"

At a meeting of the Board of Directors of the Mississippi Valley Medical Society, November 23, 1941, Dr Dan G Stine, F A C P, Columbia, Mo, was named President for 1942 Dr F Garm Norbury, F A C P, Jacksonville, Ill, was named Second Vice-President and Dr Harold Swanberg, F A C P, Quincy, Ill, was reelected Secretary-Treasurer

Dr Nathan S Davis, III, F A C P, Chicago, Ill, and Dr John H Peck, F A C P, Oakdale, Iowa, were elected to membership on the Board of Directors

Dr S A Slater was reelected president of the Minnesota Public Health Association for the fifth consecutive term at the annual meeting of the organization in St Paul recently

Dr Robert T Terry (Associate), of the Letterman General Hospital, San Francisco, Calif, is incorrectly listed in the 1941 Directory of the American College of Physicians as being in the Medical Corps of the U S Army, whereas, he is a member of the Medical Reserve Corps of the Army, on active duty Before entering active service he was in practice at Denver, Colo

Dr Joseph S D'Antoni (Associate), New Orleans, La, was chosen Vice President of the American Society of Tropical Medicine at its meeting November 10-13, 1941, in St Louis, Mo

At the recent meeting of the American Clinical and Climatological Association, Dr C Sidney Burwell, F A C P, Boston, Mass, was named President, and Dr Maurice C Pincoffs, F A C P, Baltimore, Md, and Dr Francis M Rackemann, F A C P, Boston, Mass, Vice-Presidents

Dr Willard C Rappleye, F A C P, Commissioner of Hospitals of the City of New York and Dean and Professor of Medical Economics at Columbia University College of Physicians and Surgeons, has been elected President of the Josiah Macy Jr Foundation This Foundation was organized to further medical education

Dr Joseph H Barach, Pittsburgh, Pa , addressed the Lackawanna County Medical Society on November 25, 1941 His topic was "Pneumonia " On December 2, 1941, he spoke before the Westmoreland County Medical Society on "Diabetes and Its Complications "

NEW ELECTIONS TO COLLEGE MEMBERSHIP

At a meeting of the Board of Regents December 14, 1941, at the headquarters building, Philadelphia, the following candidates were regularly elected to the class indicated

ELECTIONS TO FELLOWSHIP

December 14, 1941

Fellowship Candidates

Sponsors

ARKANSAS

John Herman Baird, North Little Rock

William B Grayson, John R Dibrell, Oliver C Melson

CALIFORNIA

Horace Bicknell Cates, Los Angeles

E Richmond Ware, Ernest C Fishbaugh, Roy E Thomas

COLORADO

Charles Douglas Deeds, Denver

Constantine F Kemper, James R Arneill, James J. Waring

Abe Ravin, Denver

John G Ryan, Rudolph W Arndt, James J Waring

Alfred Martin Wolfe, Denver

Thomas D Cunningham, James R Arneill, James J Waring

John I Zarit, Denver

Mathew A Spangelberger, Harry Gauss, James J Waring

CONNECTICUT

Charles Tiffany Bingham, Hartford

G Gardiner Russell, John A Wentworth, Charles H Turkington

Peter J Steincrohn, Hartford

Orin R Witter, Otto G Wiedman, Charles H Turkington

Charles Russman, Middletown

Roy L. Leak, F Erwin Tracy, Charles H Turkington

Robert Hough Jordan, New Haven

Theodore S Evans, Charles J Bartlett, Charles H Turkington

William Thomas Salter, New Haven

George R Minot, J H Means, William B Breed

DELAWARE

John William Pendleton Love, New Castle

George H Gehrmann, Bartholomew M Allen, Lewis B Flinn

DISTRICT OF COLUMBIA

Worth Bagley Daniels, Washington

Matthew W Perry, James P. Leake, Wallace M Yater

Leon Stuart Gordon, Washington

Tomás Cajigas, William Gerry Morgan, Wallace M Yater

MEDICAL CORPS, U S ARMY

Clifford Gordon Blitch, Washington, D C

James C Magee

MEDICAL CORPS, U S NAVY

George Brackett Dowling, San Francisco, Calif

Roy J Leutscher, Joel J White, Ross T McIntire

Edward Patrick McLarney, Jacksonville, Fla

Ross T McIntire

*Fellowship Candidates**Sponsors*

U S PUBLIC HEALTH SERVICE

Guy Henry Faget, Carville, La	Thomas Parran
Alvin Randolph Sweeney, Ellis Island,	Thomas Parran
N Y	

FLORIDA

Theodore Ferdinand Hahn, Jr, DeLand	Louie M Limbaugh, J Webster Merritt, T Z Cason
Karl Boyles Hanson, Jacksonville	Louie M Limbaugh, J Webster Merritt, T Z Cason
Lincoln Sydnor Lafitte, Jacksonville	Louie M Limbaugh, James L Borland, T Z Cason
Franz Hahr Stewart, Miami	Paul B Welch, Mathew J Flipse, T Z Cason
Paul Kasth Jenkins, Miami Beach	Charles F Roche, Robert M Harris, T Z Cason

GEORGIA

Bernard Preston Wolf, Atlanta	T Sterling Claiborne, Roy S Leadingham, Glenville Giddings
Richard Hugh Wood, Atlanta	H Cliff Sauls, Carter Smith, Glenville Giddings
Hervey Milton Clecklev, Augusta	Virgil P Sydenstricker, Joseph D Gray, Glenville Giddings
George Leonard Walker, Griffin	Trimble Johnson, Hal M Davison, Glenville Giddings

ILLINOIS

Jay Bailey Carter, Chicago	Willard O Thompson, Lee C Gatewood, LeRoy H Sloan
Israel Davidsohn, Chicago	Josiah J Moore, Malcolm T MacEachern, LeRoy H Sloan
Frank B Queen, Chicago	Rudolph W Arndt, John G Ryan, James J Waring
Willard Leo Wood, Chicago	Willard O Thompson, Lee C Gatewood, LeRoy H Sloan
Paul Spottswood Rhoads, Evanston	James G Carr, Samuel J Lang, LeRoy H Sloan
Eugene Fagan Trout, Oak Park	Willard O Thompson, Lee C Gatewood, LeRoy H Sloan

INDIANA

Ralph Ulrich Leser, Indianapolis	Edgar F Kiser, Rollin H Moser, Robert M Moore
----------------------------------	---

IOWA

James Leon Dubrow, Des Moines	Walter L Biering, John H Peck, Fred M Smith
-------------------------------	---

KANSAS

John Lewis Kleinheksel, Wichita	Henry N Tihen, Fred J McEwen, Harold H Jones
Earl Lee Mills, Wichita	Thomas T Holt, Henry N Tihen, Harold H Jones

KENTUCKY

Luther Bach, Newport	William E Gardner, Arthur C McCarty, C W Dowden
----------------------	---

LOUISIANA

Donovan Clarence Browne, New Orleans	Randolph Lyons, John H Musser, Joseph E Knighton
George Edward Burch, New Orleans	John H Musser, Grace A Goldsmith, Joseph E Knighton
Elliston Farrell, New Orleans	Tasker Howard, J Hamilton Crawford, C F Tenney, Joseph E Knighton

Fellowship Candidates

William Howard Gillentine, New Orleans
 Herbert John Schattenberg, New Orleans
 William Anthony Sodeman, New Orleans

Sponsors

John H. Musser, Philip H. Jones, Jr., Joseph I. Knighton
 John H. Musser, Philip H. Jones, Jr., Joseph I. Knighton
 John H. Musser, Grace A. Goldsmith, Joseph I. Knighton

MARYLAND

Robert William Garis, Baltimore
 Henry Mathies Hensen, Baltimore
 Charles Franklin Mohr, Baltimore
 Hugh Grigsby Whitehead, Baltimore

Sydney R. Miller, Edwin B. Jarrett, Louis Kraus
 Wetherbee Fort, Sydney R. Miller, Louis Kraus
 Wetherbee Fort, Edwin B. Jarrett, Louis Kraus
 Louis Hamman, Sydney R. Miller, Louis Kraus

MASSACHUSETTS

George Parkman Denny, Boston
 Burton Everett Hamilton, Boston
 William Timothy O'Halloran, Boston
 Richard Pratt Stetson, Boston
 Lowrey Frederick Davenport, Brookline

Albert A. Hornoi, James H. Townsend, William B. Breed
 Elliott P. Joslin, Howard F. Root, William B. Breed
 John A. Folev, James M. Faulkner, William B. Breed
 George R. Minot, J. H. Means, William B. Breed
 Donald S. King, Dwight L. Siscoe, William B. Breed

MICHIGAN

Sidney Adler, Detroit
 Emil M. Shebesta, Detroit
 Lloyd Bennett Young, Detroit

Hugo A. Freund, Edward D. Spalding, Henry R. Carstens
 Rollin H. Stevens, Charles E. Lemmon, Henry R. Carstens
 George B. Hoops, Rollin H. Stevens, Henry R. Carstens

MINNESOTA

Arthur Carl Kerkhof, Minneapolis
 Alexander Robinson MacLean, Rochester
 Edward Frank Rosenberg, Rochester
 Jan Henrik Tillisch, Rochester

S. Marx White, Harry E. Ungerleider, Edgar V. Allen
 Albert M. Snell, Henry W. Woltman, Edgar V. Allen
 Philip S. Hench, Albert M. Snell, Edgar V. Allen
 Harold C. Haben, Nelson W. Barker, Edgar V. Allen

MISSISSIPPI

Wesley Wayne Lake, Pass Christian

Ben R. Heninger, Randolph Lyons, John G. Archer

MISSOURI

William Byrne Brown, Columbia
 Carl Vernon Moore, Jr., St. Louis
 Francis Bacon Camp, Springfield

Dan G. Stine, Howard A. Rusk, A. Comingo Griffith
 Harry L. Alexander, Louis H. Behrens, David F. Barr, A. Comingo Griffith
 G. Bruce Lemmon, Elmer E. Glenn, A. Comingo Griffith

MONTANA

Alf Cornelius Johnson, Great Falls
 Thomas Franklin Walker, Great Falls

Harold W. Gregg, Malcolm D. Winter, Ernest D. Hitchcock
 Richard B. Durnin, Harold W. Gregg, Ernest D. Hitchcock

NEW HAMPSHIRE

Harold David Levine, Bristol

Henry A. Christian, Colin C. Stewart, Robert B. Kerr

*Fellowship Candidates**Sponsors*

Nathan Townley Milliken, Hanover

Harry I French, Colin C Stewart, Robert B Keri

NEW JERSEY

Samuel Cohen, Jersey City

Thomas J White, J Burns Amberson, Jr, George H Lathrope

Samuel Irving Kooperstein, Jersey City

Abraham E Jaffin, Berthold S Pollak, George H Lathrope

Charles Andrew Landshof, Jersey City

Thomas J White, Harry J Perlberg, George H Lathrope

Elizabeth Brakeley, Montclair

Harvey M Ewing, Irving S Wright, George H Lathrope

William George Bernhard, Newark

John W Gray, Edward C Klein, Jr, George H Lathrope

NEW MEXICO

Walter Ignatius Werner, Albuquerque

Ralph W Mendelson, John R Van Atta, LeRoy S Peters

NEW YORK

Saverio Charles Franco, Brooklyn

Albert F R Andresen, Frederick Schroeder, C F Tenney

Alfred Peter Ingegno, Brooklyn

Tasker Howard, Albert F R Andresen, C F Tenney

Emanuel Schwartz, Brooklyn

Albert F R Andresen, Tasker Howard, C F Tenney

Ramsdell Gurney, Buffalo

Abraham H Aaron, Stockton Kimball, Nelson G Russell

Lawrence Edgar Hummel, Buffalo

Abraham H Aaron, Clayton W Greene, Nelson G Russell

Francis Emmett Kenny, Buffalo

Walter H Krombein, Harvey C Schneider, Nelson G Russell

Dwight Turney Bonham, Hempstead

Willard J Davies, Louis H Bauer, C F Tenney

Benjamin Roy Allison, Hewlett

Henry T Chickering, Russell L Cecil, C F Tenney

Jacob Ernest Nadler, Jackson Heights

Arthur C DeGraff, Norman Jolliffe, C F Tenney

Harold Albert Butman, Manhasset

Louis H Bauer, Willard J Davies, C F Tenney

Alexander John Chilko, New Rochelle

Arthur F Heyl, George W Cramp, C F Tenney

Arthur Joseph Antenucci, New York

Howard F Shattuck, Asa L Lincoln, C F Tenney

Harold Brandalone, New York

Elaine P Ralli, Norman Jolliffe, C F Tenney

Frank Miller Falconer, New York

Howard F Shattuck, Peter Irving, C F Tenney

John Alexander Clinton Gray, New York

Howard F Shattuck, Robert A Cooke, C F Tenney

William Hall Lewis, Jr, New York

Asa L Lincoln, Cornelius P Rhoads, C F Tenney

Putnam Crocker Lloyd, New York

William W Herrick, Randolph West, Walter W Palmer, C F Tenney

Walter Lindsay Niles, New York

Robert A Cooke, George Morris Piersol, C F Tenney

Leon Arthur Salmon, New York

Charles A McKendree, A Wilbur Duryee, C F Tenney

Christopher Parnall, Jr, Rochester

David B Jewett, Charles B F Gibbs, Nelson G Russell

Daniel Milton Brumfiel, Saranac Lake

John N Haves, William S McCann, Nelson G Russell

Walter Carl Hausheer, Staten Island

Arthur C DeGraff, George G Ornstein, James Alex Miller, C F Tenney

John Michael Nicklas, Trudeau

John K Deegan, J Burns Amberson, Jr, C F Tenney

Thomas Douglas Kendrick, Utica

Andrew Sloan, William A Groat, Nelson G Russell

Charles Wesley Martin, Woodmere

Louis H Bauer, Louis A Van Kleeck, C F Tenney

*Fellowship Candidates**Sponsors*

NORTH CAROLINA

Charles Darwin Thomas, Sanatorium

Paul P. McCain, William T. Rainey, C. H. Cocke

NORTH DAKOTA

Paul Jean Breslich, Minot

Paul H. Rowe, Robert B. Radl, Julius O. Anson

OHIO

Arthur Dale Nichol, Cleveland
Ruth Alice Koons, Columbus
Lewis Keir Reed, YoungstownCharles T. Way, Harry D. Piercy, A. B. Brower
R. W. Kissane, Charles A. Doan, A. B. Brower
William H. Bunn, Colin R. Clark, Roy W. Scott,
A. B. Brower

OKLAHOMA

Richard Michael Burke, Clinton
Minard Friedberg Jacobs, Oklahoma City
Samuel Goodman, TulsaFrank L. Jennings, Ben H. Cooley, Lea A. Riely
Wann Langston, John E. Heatley, Lea A. Riely
Russell C. Pigford, Homer A. Ruprecht, Lea A.
Riely

OREGON

Max William Hemingway, Bend

Ernest L. Boylen, John H. Fitzgibbon, Homer P.
Rush

Irvin Reginald Fox, Eugene

Fredrick A. Willius, Albert H. Ross, Homer P.
Rush

Guy Robert McCutchan, Portland

William E. Ash, Aldis A. Johnson, Homer P. Rush

PENNSYLVANIA

Alfred Winfield Dubbs, Allentown

Thomas Klein, Willard D. Kline, Edward L.
Bortz

Abraham Max Balter, Aspinwall

Kelso A. Carroll, Charles M. Griffith, R. R.
Snowden

William Freas Confair, Benton

William Devitt, Harold L. Tonkin, Edward L.
BortzClaude Wilber Ashley, Bloomsburg
Robert Deming Donaldson, KaneCarl E. Ervin, Arthur E. Davis, Edward L. Bortz
George J. Kastlin, James M. Strang, R. R.
Snowden

William Osler Abbott, Philadelphia

T. Grier Miller, Charles C. Wolferth, Edward L.
Bortz

Theodore Lyle Hazlett, Pittsburgh

C. Howard Marcy, Howard G. Schleiter, R. R.
Snowden

RHODE ISLAND

Cecil Calvert Dustin, Providence

Henry L. C. Weyler, Isaac Geibel, Alex. M.
Burgess

Robert Gordon Murphy, Providence

Charles F. Goinly, Herman A. Lawson, Alex. M.
Burgess

TENNESSEE

Carl Adam Hartung, Chattanooga

James L. Bibb, Franklin B. Bogart, William C.
Chaney

Wallace Lamar Poole, Johnson City

Frank L. Roberts, Horton R. Casparis, J. O.
Manier

TEXAS

Max Erwin Suehs, Beaumont
Cecil Overton Patterson, DallasLee T. Pruitt, Victor M. Longmire, M. D. Levy
David W. Carter, Jr., Milford O. Rouse, M. D.
Levy

Lloyd Webster Sheekles, Jr., Galveston

George R. Herrmann, Raymond L. Gregory,
M. D. Levy

Edward Albert Wilkerson, Houston

Frederick R. Lummis, LeRoy B. Duggan, M. D.
Levy

In 1860 the Saint Paul Academy of Medicine and Surgery, our first local medical society, was formed. It was a most successful organization. A medical library was established, a laboratory put in operation, and a microscope and an electrical machine purchased. Some instruction to medical students was also given by its members in its halls. Unfortunately for this society, the Civil War interfered with its functions as all its members went into the army. When the war was over many new practitioners had settled in Saint Paul, and it was thought that since the members of the Academy could not take in the newcomers without sacrificing their funds, and since all had to recoup their fortunes, it would be wisest to disband. The lot that had been purchased for a home was sold, the books in the library returned to the donors, and the laboratory apparatus disposed of.

Informal medical meetings were held here until our Ramsey County Medical Society was organized in 1870, a year later than our present State Association. Since then our Society has had a prosperous career and many local and special medical societies have been organized.

Medical journalism and medical teaching started in Minnesota this same year, 1870, with the establishment of the Northwestern Medical and Surgical Journals, and the opening of the Saint Paul Medical College in Saint Paul by Dr. Alexander J. Stone. The journal, a quarterly, lasted four years and the Medical School until 1888 when the medical department of the University of Minnesota was established in Minneapolis with practically the entire teaching staff of the Saint Paul School on the faculty.

Since 1870 Saint Paul has been well known as a medical center, and many eminent physicians have practiced their profession here. The Medical Journal now known as the Journal-Lancet, was established in Saint Paul by Dr. Stone in 1881, but is now published in Minneapolis.

In 1899 the Saint Paul Medical Journal was started by the Ramsey County Medical Society and continued until 1917 when "Minnesota Medicine," the organ of the State Medical Association, was established, the Saint Paul Journal agreeing to disband its publication to protect the new journal.

The Ramsey County Medical Society has, since 1899, a well equipped and maintained medical library, adequately housed and supported, with a trained medical librarian in charge and containing 25,000 books and bound journals. The funds to support this library are derived from interest on a fund accumulated from the sale and manufacture of surgical ligatures, which enterprise was started by Dr. Edward Boeckmann over 40 years ago, and also from profits from the now defunct Saint Paul Medical Journal.

The medical practitioners of Saint Paul are proud of their past history and optimistic that their professional standing for the future is assured.

HISTORY OF PIONEER MEDICAL PRACTICE IN ST. PAUL *

By J M ARMSTRONG

IN the year 1847, Dr John Jay Dewey established himself at Saint Paul's Landing, now known as Saint Paul. Dr Dewey was a younger brother of the Governor of Wisconsin Territory and as Wisconsin was about to become a state, it was surmised that a new territory would be set up to the west, and that the capitol of the new territory would be a desirable place to settle. This we believe was the reason that influenced Dewey to come here.

At that time our population numbered about forty. Dr Dewey was a man of 25, had graduated from the Albany Medical College in March of that year, and remained here until his death in 1891.

When Minnesota Territory was established in 1849 with Saint Paul as its capitol, the town took on a rapid growth, there being about 300 inhabitants by the end of the year, and the number of physicians increased to six. Dr Thomas R. Potts became the first president of the Trustees of the town, and Dr David Day, Register of Deeds. Both these men were graduates of the University of Pennsylvania and both resided here the rest of their lives.

From this time on the town increased rapidly in population and not a few medical men made a trial of the practice of their professions here. Many of them remained but a short time, moving to other parts of the territory as settlement progressed.

In 1853 the first medical society in the territory was organized in Saint Paul, called "The Minnesota Medical Society." At that time there were about 20 medical men in the territory, and 13 of them responded to the call of the organizers. This society lived until 1857, when the last annual meeting was held in St. Ansbury, now part of Minneapolis. The financial panic of that year undoubtedly was the cause of its demise.

In 1850, Saint Paul had a population of 10,279, so one can see that growth was considerable. However, fur trading, the exportation of pine lumber and cranberries were the only industries.

In the year 1853, the cornerstone of our first hospital, and the first in the territory, was laid, but it did not open for patients until 1855. In 1854 and 1855 our city was invaded by an epidemic of Asiatic cholera which took its toll of both immigrants and residents, and put a severe test on the town.

In 1857 the predecessor of St. Luke's Hospital was established. It was not until many years later that other hospitals which now number 16 were established. At present these hospitals can care for 2,863 patients, and have 261 bassinets.

* The American College of Physicians will hold its Twenty-Sixth Annual Session in St. Paul, April 20-24, 1942.

transferred in December 1923 to the post of assistant to the Surgeon, Sixth Corps Area in Chicago. Always a keen student of internal medicine, he was detailed in December 1927 to Beaumont General Hospital as head of the medical service. In 1932 he was transferred to a similar position in the Walter Reed Hospital in Washington. A recent duty was the command of Gorgas Hospital at Ancon in the Canal Zone, from which service he returned in August 1941, taking over the place in the Corps Area Headquarters at Baltimore.

Colonel Dailey was one of the Army's notable specialists in internal medicine. His preparation for this work included a course at the Mayo Clinic. He was a fellow of the American College of Physicians and a diplomat of the American Board of Internal Medicine.

Colonel Dailey was married to Joen Margaret O'Brien, who with two sons and a daughter, survives him.

A large funeral cortege accompanied the remains from Baltimore to the Memorial Chapel at the Army Medical Center on October 30, where services were conducted by Chaplain Edward J. McTague of Walter Reed Hospital. Interment was in Arlington National Cemetery.

*Fellowship Candidates**Sponsors*

NORTH CAROLINA

Charles Darwin Thomas, Sanatorium

Paul P McCain, William T Rainey, C II Cocke

NORTH DAKOTA

Paul Jean Breslich, Minot

Paul H Rowe, Robert B Radl, Julius O Arnsen

OHIO

Arthur Dale Nichol, Cleveland

Ruth Alice Koons, Columbus

Lewis Kerr Reed, Youngstown

Charles T Way, Harry D Piercy, A B Brower

R W Kissane, Charles A Doan, A B Brower

William H Bunn, Colin R Clark, Roy W Scott,
A B Brower

OKLAHOMA

Richard Michael Burke, Clinton

Minard Friedberg Jacobs, Oklahoma City

Samuel Goodman, Tulsa

Frank L Jennings, Ben H Cooley, Lea A Riely

Wann Langston, John E Heatley, Lea A Riely

Russell C Pigford, Homer A Ruprecht, Lea A
Riely

OREGON

Max William Hemingway, Bend

Ernest L Boylen, John H Fitzgibbon, Homer P
Rush

Irvin Reginald Fox, Eugene

Fredrick A Willius, Albert H Ross, Homer P
Rush

Guy Robert McCutchan, Portland

William E Ash, Aldis A Johnson, Homer P Rush

PENNSYLVANIA

Alfred Winfield Dubbs, Allentown

Thomas Klein, Willard D Kline, Edward L
Bortz

Abraham Max Balter, Aspinwall

Kelso A Carroll, Charles M Griffith, R R
Snowden

William Freas Confair, Benton

William Devitt, Harold L Tonkin, Edward L
Bortz

Claude Wilber Ashley, Bloomsburg

Carl E Ervin, Arthur E Davis, Edward L Bortz

Robert Deming Donaldson, Kane

George J Kastlin, James M Strang, R R
Snowden

William Osler Abbott, Philadelphia

T Grier Miller, Charles C Wolferth, Edward L
Bortz

Theodore Lyle Hazlett, Pittsburgh

C Howard Marcy, Howard G Schleiter, R R
Snowden

RHODE ISLAND

Cecil Calvert Dustin, Providence

Henry L C Weyler, Isaac Gerber, Alex M
Burgess

Robert Gordon Murphy, Providence

Charles F Gormly, Herman A Lawson, Alex M
Burgess

TENNESSEE

Carl Adam Hartung, Chattanooga

James L Bibb, Franklin B Bogart, William C
Chaney

Wallace Lamar Poole, Johnson City

Frank L Roberts, Horton R Casparis, J O
Manier

TEXAS

Max Erwin Suehs, Beaumont

Lee T Pruitt, Victor M Longmire, M D Levy

Cecil Overton Patterson, Dallas

David W Carter, Jr, Milford O Rouse, M D
Levy

Lloyd Webster Sheckles, Jr, Galveston

George R Herrmann, Raymond L Gregory,
M D Levy

Edward Albert Wilkerson, Houston

Frederick R Lummis, LeRoy B Duggan, M D
Levy

*Fellowship Candidates**Sponsors*

VIRGINIA

Walter Lewis Nalls, Richmond

Dean B Cole, R Finley Gayle, Jr, Walter B Martin

John Braxton McKee, Winchester

Dean B Cole, R Finley Gayle, Jr, Walter B Martin

WASHINGTON

Donald Ainslie Palmer, Spokane

George H Anderson, Edwin G Bannick, Charles E Watts

Max Singer Wright, Spokane

George H Anderson, Carl S Leede, Charles E Watts

REPUBLIC OF PANAMA

Amadeo Vicente-Mastellari, Panama

Henry C Dooling, Tomás Guardia, William M James

CHINA

Frederick Gilman Scovel, Tsining

Chester N Frazier, Henry S Houghton, Henry M Thomas, Jr

"RESOLVED, that the following list of 5 be and herewith are elected to Fellowship in the American College of Physicians as of April 19, 1942"

CALIFORNIA

Archie Marvin Roberts, Los Angeles

E Richmond Ware, George H Houck, Roy E Thomas

Delbert H McNamara, Santa Barbara

Harry E Henderson, Hildahl I Burtness, Roy E Thomas

MEDICAL CORPS, U S ARMY

Kenneth George Gould, Montgomery, Ala

James C Magee

U S PUBLIC HEALTH SERVICE

Clifton Keck Himmelsbach, Lexington, Ky

Thomas Parran

OHIO

Louis Bonner Owens, Cincinnati

William L Freyhof, John H Skavlem, A B Brower

ELECTIONS TO ASSOCIATESHIP

December 14, 1941

*Associateship Candidates**Sponsors*

ARKANSAS

Ely Driver Rowland, Hot Springs National Park

Samuel G Shepherd, Euclid M Smith, Oliver C Melson

Gerald Blankfort, Little Rock

Paul C Eschweiler, Euclid M Smith, Oliver C Melson

Fred William Harris, Little Rock

Paul C Eschweiler, Euclid M Smith, Oliver C Melson

CALIFORNIA

Jesse Headen Inman, Bakersfield

George H Houck, Arthur Stanley Granger, Roy E Thomas

Lawrence Arthur Williams, Pasadena
Walter Beckh, San FranciscoB O Raulston, Alvin G Foord, Roy E Thomas
Dwight L Wilbur, Arthur L Bloomfield, Ernest H Falconer

Richard Dufficy Friedlander, San Francisco

Dudley W Bennett, Stacy R Mettier, Ernest H Falconer

John Orren Vaughn, Santa Monica

Roland Cummings, Raymond Sands, Roy E Thomas

*Associateship Candidates**Sponsors*

COLORADO

David Wilson McCarty, Jr, Longmont

Clough Turrill Burnett, James R Arneill, James J Waring

CONNECTICUT

Samuel Nesbitt, New Haven

Albert M Snell, Samuel F Haines, Edgar V Allen, Charles H Turkington

DISTRICT OF COLUMBIA

George James Stuart, Washington

Matthew W Perry, Walter A Bloedorn, Wallace M Yater

MEDICAL CORPS, U S ARMY

John Kemp Davis, Washington, D C

James C Magee

William Bell Foster, Washington, D C

James C Magee

Floyd Vern Kilgore, Fort Sill, Okla

James C Magee

Dwight Lawson, Hot Springs National Park, Ark

James C Magee

David Ernest Liston, Takoma Park, D C

James C Magee

George Barnard Moore, Jr, Camp Claiborne, La

William C Pollock, George F Aycock, James C Magee

Ernest Holden Parsons, Atlanta, Ga

James C Magee

Arthur Eugene White, Hot Springs National Park, Ark

James C Magee

MEDICAL CORPS, U S NAVY

Cecil Lenzora Andrews, San Diego, Calif

Joel J White, Roy J Leutscher, Ross T McIntire

Leon Delwin Carson, Washington, D C

John R Poppen, E Richison, Ross T McIntire

Vincent Hernandez, Washington, D C

John Harper, E Richison, Ross T McIntire

Jerome Frost Smith, San Diego, Calif

Joel J White, Roy J Leutscher, Ross T McIntire

U S PUBLIC HEALTH SERVICE

Gordon Arthur Abbott, Stapleton, Staten Island, N Y

Thomas Parran

Kenneth William Chapman, Lewisburg, Pa

Thomas Parran

Thomas Royle Dawber, Boston, Mass

Thomas Parran

Waldemar Claus Dreessen, Bethesda, Md

Thomas Parran

Robert Harrold Flinn, Bethesda, Md

Thomas Parran

Eugene Willard Green, Springfield, Mo

Thomas Parran

William David King, San Francisco, Calif

Thomas Parran

Harold Dwight Lyman, Springfield, Mo

Thomas Parran

Albert Taylor Morrison, Galveston, Tex

Thomas Parran

Kenneth Roy Nelson, Baltimore, Md

Thomas Parran

William Frederick Ossenfort, Fort Worth, Tex

Thomas Parran

Frank Lewis Price, Ellis Island, N Y

Thomas Parran

Edward Clinton Rinck, Lewisburg, Pa

Thomas Parran

James Raymond Shaw, San Francisco, Calif

Thomas Parran

James Gavin Telfer, Chicago, Ill

Thomas Parran

FLORIDA

Jere Wright Annis, Lakeland

Webster Merritt, William C Blake, T Z Cason

GEORGIA

Robert Bruce Logue, Atlanta

Carter Smith, H Cliff Sauls, Glenville Giddings

ILLINOIS

Harry Allen Warren, Champaign

Lyman H Hoyt, Soma Weiss, LeRoy H Sloan

Paul Lawrence Shallenberger, Chicago

Arthur E Mahle, J Roscoe Miller, LeRoy H Sloan

Benjamin Harold Neiman, Oak Park

Maurice Lewison, Isadore M Trace, LeRoy H Sloan

IOWA

John William Grant Caldwell, Des Moines

Daniel J Glomset, Walter L Bierring, Fred M. Smith

*Issociateship Candidates**Sponsors*

Lee H Leger, Kansas City

KANSAS

Fred E Angle, William H Algie, Harold H Jones

James Robert Hendon, Louisville

KENTUCKY

Frederick G Speidel, Oscar O Miller, C W Dowden

Norton William Voorhies, New Orleans

LOUISIANA

Philip H Jones, Jr, Julius L Wilson, Joseph E Knighton

Madelaine Ray Brown, Boston

MASSACHUSETTS

J H Means, Earle M Chapman, William B Breed

Milton Henry Clifford, Boston

Wyman Richardson, Thomas V Urmy, William B Breed

Eugene Charles Eppinger, Boston

C Sidney Burwell, Samuel A Levine, Reginald Fitz, William B Breed

Charles Folsom Walcott, Cambridge

Conrad Wesselhoeft, James M Faulkner, William B Breed

Henry Dows Stebbins, Marblehead

J H Means, Walter Bauer, William B Breed

John Francis McManus, Newton

John A Foley, Chester S Keefer, William B Breed

Charley Johnson Smyth, Eloise

MICHIGAN

Cyrus C Sturgis, Herman H Riecker, Henry R Carstens

Glenn Edward Drewyer, Flint

Franklin W Baske, Myrton S Chambers, Henry R Carstens

Randall George Sprague, Rochester

MINNESOTA

Edward H Rynearson, Samuel F Haines, Edgar V Allen

Joseph Maurice Ryan, St Paul

Harold Edward Richardson, John A. Lepak, Edgar V Allen

Joseph Israel Echikson, Newark

NEW JERSEY

Frederic A Alling, Edward C Klein, Jr, George H Lathrope

John Edward Leach, Paterson

Cornelius P Rhoads, Lloyd F Craver, C F Tenney, George H Lathrope

Edgar Ernest Evans, Penns Grove

Thomas M Kam, Ralph K Hollinshed, George H Lathrope

Norman Lovell Murray, Summit

Harvey M Ewing, Dean W Marquis, George H Lathrope

Peter James Warter, Trenton

Stanley P Reimann, John W Gray, George H Lathrope

Adele Emily Streeseman, Brooklyn

NEW YORK

Carl H Greene, James Alex Miller, George Morris Piersol, C F Tenney

Charles Stewart Wallace, Ithaca

Norman S Moore, Frederick Beck, Nelson G Russell

William Chester, Mamaroneck

John L Kantor, Bernard S Oppenheimer, C F Tenney

Julius Chasnoff, New York

Thomas H McGavack, Linn J Boyd, C F Tenney

Willis Aloysius Murphy, New York

Asa L Lincoln, Benjamin I Ashe, C F Tenney

Carl Reich, New York

James R Lisa, David Stanley Likely, C F Tenney

William Dorus Stubenbord, New York
Frederick Thomas Zimmerman, New YorkAsa L Lincoln, Benjamin I Ashe, C F Tenney
Hiland L Flowers, Charles M Griffith, C F Tenney

John Charles Leonard, Rye

George Blumer, Arthur Bliss Davton, Charles H Turkington, C F Tenney

*Associateship Candidates**Sponsors*

NORTH CAROLINA

William Gardner Morgan, Chapel Hill
 Robert Edwards Stone, Chapel Hill
 William Hamilton Roper, Sanatorium

W Reece Berryhill, Groesbeck Walsh, C H Cocke
 William deB. MacNider, Tom D Spies, C H Cocke
 Paul P McCain, W Reece Berryhill, C H Cocke

OHIO

Roswell Schiedt Fidler, Columbus
 Robert Chester Kirk, Columbus
 Marion Noville Gibbons, Shaker Heights

R W Kissane, H V Weirauk, A B Brower
 Jacob Jones Coons, Charles A Doan, A B Brower
 Harold Feil, Harley A Williams, A B Brower

OKLAHOMA

Owen Royce, Jr, Oklahoma City

Wann Langston, E R Musick, Lea A Riely

OREGON

Vernon Eldred Fowler, Astoria
 Frank Perlman, Portland
 Frank Kenneth Power, Salem

Ernest L Boylen, John H Fitzgibbon, T Homer Coffen, Homes P Rush
 Robert L Benson, Noble Wiley Jones, Homer P Rush
 Ernest L Boylen, T Homer Coffen, Homer P Rush

PENNSYLVANIA

Charles LeRoy Mengel, Allentown
 Louis Clair Burket, Altoona
 Maximo Joseph Tornatore, Clearfield
 Charles William Smith, Harrisburg
 Robert Pratt McCombs, Philadelphia
 Stoughton Ralph Vogel, Philadelphia
 George Ransom Taylor, Philipsburg
 Wilton Ross Glenney, Pottsville

Willard D Kline, Clyde H Kelchner, Edward L Bortz
 August S Kech, Elwood W Stitzel, R R Snowden
 George A Ricketts, George McClintock Hutchison, R R Snowden
 Carl E Ervin, John B McAlister, Edward L Bortz
 George Morris Piersol, Harry Bond Wilmer, Edward L Bortz
 Charles L Brown, W Edward Chamberlain, Edward L Bortz
 George A Ricketts, John M Johnston, R R Snowden
 Carl E Ervin, William Devitt, Edward L Bortz

TEXAS

Louie Edgar Allday, Dallas
 John Spurgeon Bagwell, Jr, Dallas
 Alfred William Harris, Dallas
 Edwin Luther Rippey, Dallas
 Newton Alvin Kilgore, Jr, Houston
 Ralph L Coffelt, Waco

David W Carter, Jr, J Shirley Sweeney, M D Levy
 Henry M Winans, Milford O Rouse, M D Levy
 David W Carter, Jr, Soma Weiss, M D Levy
 David W Carter, Jr, Milford O Rouse, M D Levy
 James H Agnew, John G Mateer, M D Levy
 I Warner Jenkins, Edward H Schwab, M D Levy

VIRGINIA

Robley Dungleison Bates, Jr, Richmond
 Morton Morris Pinckney, Richmond
 Elam Cooksey Toone, Jr

Paul D Camp, Dean B Cole, Walter B Martin
 Wyndham B Blanton, William B Porter, Walter B Martin
 William B Porter, Harry Walker, Walter B Martin

WEST VIRGINIA

Emory Hendon Main, Philippi

Edward J Van Liere, Raphael J Condry, Albert H Hoge

DOMINION OF CANADA

Ontario

Robert Williams Graham, Ottawa

Nelson W Barker, Edgar A Hines, Jr, Edgar V Allen, Warren S Lyman

1942 POSTGRADUATE COURSES OF THE AMERICAN COLLEGE OF PHYSICIANS

In the November, 1941, issue of this journal a full outline of the Program of Postgraduate Courses for 1942 was published. They are repeated here in outline only.

No 1—ALLERGY

(February 2-14, 1942)

The Roosevelt Hospital, Department of Allergy
New York, N. Y.

ROBERT A. COOKE, M.D., F.A.C.P., *Director*

This course is registered to capacity and no additional applications can be accepted.

No 2—THE DIAGNOSIS AND TREATMENT OF HEART DISEASE

(February 2-14, 1942)

Massachusetts General and other Boston Hospitals
Boston, Mass.

PAUL D. WHITE, M.D., F.A.C.P., *Director*

No 3—GENERAL MEDICINE

(February 2-14, 1942)

University of California Medical School and Stanford University School of Medicine,
San Francisco, Calif.

WILLIAM J. KERR, M.D., F.A.C.P., *Director*

STACY R. METTIER, M.D., F.A.C.P., *Associate Director*
University of California Medical School

ARTHUR L. BLOOMFIELD, M.D., F.A.C.P., *Director*

DWIGHT L. WILBUR, M.D., F.A.C.P., *Associate Director*
Stanford University School of Medicine

This course has been withdrawn due to war concern along the Pacific Coast.

No 4—INTERNAL MEDICINE

(February 2-14, 1942)

Johns Hopkins University School of Medicine and University of Maryland School of
Medicine, Baltimore, Md.

WARFIELD T. LONGCOPE, M.D., F.A.C.P., *Director*

GEORGE W. THORN, M.D., F.A.C.P., *Associate Director*
Johns Hopkins University School of Medicine

MAURICE C. PINCOFFS, M.D., F.A.C.P., *Director*

H. RAYMOND PETERS, M.D., F.A.C.P., *Associate Director*
University of Maryland School of Medicine

Although there was a very representative registration for this course, it had to be cancelled due to the fact that the Johns Hopkins Hospital Unit and a number of members of the faculty were called to active military duty, making it both impracticable and impossible to give the course.

No 5—GASTRO-INTESTINAL DISEASES

(February 2-7, 1942)

Graduate Hospital, University of Pennsylvania
Philadelphia, Pa.

HENRY L. BOCKUS, M.D., F.A.C.P., *Director*

No 6—ALLERGY

(April 6-18, 1942)

Washington University School of Medicine and
Barnes Hospital, St Louis, MoHARRY L. ALEXANDER, M D , F A C P , *Director*

This course has now been withdrawn due to some of the faculty members being called to active military service and it being impossible to get substitutes at so late a date

No 7—ARTHRITIS AND RHEUMATIC DISEASES

(April 13-18, 1942)

The Mayo Foundation, University of Minnesota, and
The Mayo Clinic, Rochester, MinnPHILIP S. HENCH, M D , F A C P , *Director*No 8—PERIPHERAL VASCULAR DISEASES, INCLUDING
HYPERTENSION

(April 6-18, 1942)

The Mayo Foundation, University of Minnesota, and
The Mayo Clinic, Rochester, MinnEDGAR V. ALLEN, M D , F A C P , *Director*

No 9—GASTRO-INTESTINAL DISEASES

(April 6-18, 1942)

University of Chicago, The School of Medicine

WALTER L. PALMER, M D , F A C P , *Director*

No 10—INTERNAL MEDICINE

(April 6-18, 1942)

University of Minnesota Medical School, Minneapolis, Minn

CECIL J. WATSON, M D , F A C P , *Director*

For several weeks this course has been filled to capacity and no additional applications can be accepted

No 11—TUBERCULOSIS

(April 13-18, 1942)

University of Colorado School of Medicine and Hospitals
Denver, ColoJAMES J. WARING, M D , F A C P , *Director*

A general bulletin announcing these courses was distributed to all members of the College during November, 1941, and a detailed outline of all courses was likewise mailed to all members early in January. It is deeply regretted that war conditions have made it necessary to alter the plans in some respects, as noted in connection with Courses No 3 and No 4. War should not be a signal, however, for the end of medical growth, but rather a challenge to greater responsibility for medical progress. Every physician owes it to himself, to his patients and to his country to know more and practice better medicine. Physicians are urged, so far as possible, to keep up their work in postgraduate education.

READING LISTS AND BIBLIOGRAPHIES

By direction of the Board of Regents the Advisory Committee on Postgraduate Courses of the College attempted to obtain reading lists for each postgraduate course for publication in this journal, making these lists available to the entire membership of the College, in addition to better preparing the men who will take the courses. Several of the Directors after a close and critical study of the texts and articles in the current literature have submitted the lists which follow. In no way are these lists to be considered all inclusive.

ALLERGY

COURSE No 1

Textbooks

- Practice of Allergy Watten T. Vaughan C. V. Mosby Co., St. Louis, 1939
 Asthma and Hay Fever in Theory and Practice A. F. Coca, M. Walzer and A. A. Thommen Charles C. Thomas, Baltimore, 1931
 Clinical Allergy Louis Tuft W. B. Saunders Co., Philadelphia, 1937
 Occupational Diseases of the Skin Louis Schwartz and Louis Tulipan Lea and Febiger, Philadelphia, 1939

Monographs

- Allergy C. E. Von Pirquet Archives of Internal Medicine 7: 259, 1911
 Anaphylaxis, Hypersensitiveness and Allergy W. W. C. Topley An Outline of Immunity, Chapter 12, p. 192 Wm. Wood Co., 1935
 Hypersensitiveness, Anaphylaxis, Allergy H. Gideon Wells The Chemical Aspects of Immunity, Chapter 9, p. 225, second edition Chemical Catalog Co., New York, 1929
 Diseases of Allergy Robert A. Cooke Chapter 21, p. 1079, Internal Medicine John H. Musser Lea and Febiger, Philadelphia, 1938, third edition
 Diseases of Allergy Robert A. Cooke Page 535, A Textbook of Medicine Russell L. Cecil W. B. Saunders Co., Philadelphia, 1940, fifth edition
 Human Sensitization Robert A. Cooke and A. Vander Veer Journal of Immunology 1: 201, 1916
 Herter Lectures H. H. Dale Bulletin Johns Hopkins Hospital 31 pps 257, 310, 373, 1920
 Anaphylaxis Carl A. Dragstedt Physiol. Rev. 21: 563, 1941
 Histamine and Anaphylaxis W. Feldberg Annual Review of Physiology, March 1941

*Articles**Immunological Basis of Sensitization*

- Horse Asthma Following Blood Transfusion M. A. Ramirez J. A. M. A. 73: 984, 1919
 Studies on the Reactions of Asthmatics and on Passive Transference of Hypersusceptibility Arent de Besche Am. J. Med. Sciences 166: 265, 1923
 Indirect Method of Testing M. Walzer J. Allergy 1: 231, 1930
 Studies in Hypersensitiveness XXXVI A Comparative Study of Antibodies Occurring in Anaphylaxis, Serum Disease and the Naturally Sensitive Man Robert A. Cooke and W. C. Spain J. Immunol. 17: 295, 1929
 Passive Sensitization of Human Skin by Serum of Experimentally Sensitized Animals W. B. Sherman, A. Stull and S. F. Hampton J. Immunology 36: 447, 1939

- Serological Evidence of Immunity with Co-existing Sensitization in a Type of Human Allergy Hay Fever R A Cooke, J H Barnard, S Hebdal and A Stull J Exper Med 62 773, 1935
- Immunological Studies of Pollinosis I The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients M. H Loveless J Immunol 38 25, 1940
- Studies in the Transmission of Sensitization from Mother to Child in Human Beings S D Bell and Z Eriksson J Immunol 20 447, 1931
- The Placental Transmission of Antibodies in the Skin-Sensitive Type of Human Allergy W B Sherman, S F Hampton and R A Cooke J Exper Med 72 611, 1940
- The Question of the Elimination of Foreign Protein (Eggwhite) in Woman's Milk H H Donnelly J Immunol 19 15, 1930
- The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin E L Burky J Allergy 5 466, 1934

General Clinical Allergy

- History Taking in Allergic Diseases F M Rackemann J A M A 106 976, 1936
- Studies in Specific Hypersensitiveness III On Constitutional Reactions The Dangers of the Diagnostic Cutaneous Test and Therapeutic Injection of Allergens R A Cooke J Immunol 7 119, 1922
- The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma Analysis of the Causative Factors F F Furstenberg and L N Gay Bull Johns Hopkins Hospital 60 412, 1937
- The Delayed Type of Allergic Reaction R A Cooke Ann Int Med 3 658, 1930
- Treatment of Allergic Disorders with Histamine and Histaminase H L Alexander J Lab & Clin Med 26 110, 1940

Asthma

- Asthma in Children R A Cooke J A M A 102 664, 1934
- Infective Asthma Indication of Its Allergic Nature R A Cooke Am J Med Sci 183 309, 1932
- Relation of Asthma to Sinusitis with Special Reference to the Results from Surgical Treatment R A Cooke and R C Grove Arch Int Med 56 779, 1935
- The Pathology of Bronchial Asthma H L Huber and K K Koessler Arch Int Med 30 689, 1922
- Effects on Heart of Long Standing Bronchial Asthma H L Alexander, D Luten and W B Kountz J A M A 88 882, 1927
- Deaths from Bronchial Asthma W B Kountz and H L Alexander Arch Path 5 1003, 1928
- Studies in Specific Hypersensitiveness IV New Etiologic Factors in Bronchial Asthma R A Cooke J Immunol 7 147, 1922
- Asthma Due to a Fungus-Alternaria J. G Hopkins, R W Denham and B M Kesten J A M A 94 6, 1930

Nasal Allergies

- Seasonal Hay Fever and Asthma Due to Molds S M Feinberg J A M A 107 1861, 1936
- Importance of Allergy in Etiology and Treatment of Nasal Mucous Polyps R A Kern J A M A 103 1293, 1934
- The Preparation and Standardization of Pollen Extracts for the Treatment of Hay Fever R A Cooke and A Stull J Allergy 4 87, 1933

- New Plan for Applying Specific Treatment of Pollen Hay Fever (Perennial Treatment) Aaron Brown J Immunol 13 273, 1927
 The Relative Merits of Seasonal and Perennial Treatment of Hay Fever A Vander Veer J Allergy 7 578, 1936
 Calculating Pollen Concentration of the Air E C Cocke J Allergy 8 601, 1937
 Evaluation of the Ragweed Hay Fever Resort Areas of North America O C Durham J Allergy 8 175, 1937

Intestinal Allergy

- Gastro-intestinal Manifestations of Allergy R A Cooke Bull N Y Acad Med Second Series IX 15, 1933
 Food Idiosyncrasy as a Factor of Importance in Gastro-enterology and in Allergy W T Vaughan Rev Gastroenterol 5 1, 1938

Skin Allergy

- A Tentative Classification of Allergic Dermatoses M B Sulzberger, F Wise and J Wolf J A M A 104 1489, 1935
 A Critical Review of 170 Cases of Urticaria and Angioneurotic Edema Followed for a Period of from Two to Ten Years A I Fink and L N Gay J Allergy 5 615, 1934
 Eczema L W Hill Vol IV, Chapter 43, Brenneman's Practice of Pediatrics W F Prior Co, Hagerstown, Md
 Studies in Specific Hypersensitiveness XXVII Dermatitis Venenata Toxicodendron Radicans W C Spain and R A Cooke J Immunol 13 93, 1927
 Report of the Investigation and Successful Treatment (Preventive) of Dermatitis Resulting from the Handling of Tulip Bulbs A H W Caulfield J Allergy 8 181, 1937

Miscellaneous Allergy

- Cerebral Symptoms Induced by Angioneurotic Edema F Kennedy Arch Neurol and Psychiat 15 28, 1926
 Allergic Migraine W T Vaughan J A M A 88 1983, 1927
 Food Allergy in Henoch's Purpura H L Alexander and C H Eyermann Arch Dermat & Syph 16 332, 1927
 The Clinical Diagnosis of Periarthritis Nodosa M B Cohen, B S Kline and A M Young J A M A 107 1555, 1936
 Allergy Induced by Immunization with Tetanus Toxoid R A Cooke, S F Hampton, W B Sherman and A Stull J A M A 114 1854, 1940
 Elimination of Horse Serum Specificity from Antitoxins R D Coghill, N Fell, M Creighton and G Brown J Immunol 39 207, 1940
 Physical Allergy W W Duke J A M A 84 736, 1925
 Allergy in Drug Idiosyncrasy R A Cooke J A M A 73 759, 1919

THE DIAGNOSIS AND TREATMENT OF HEART DISEASE

COURSE No 2

- Tandler, J Anatomie des Herzens, Gustav Fischer, Jena, 1913
 Wiggers, C J Physiology in Health and Disease 3rd edition Lea & Febiger, Philadelphia, 1939
 Lewis, Thomas The Mechanism and Graphic Registration of the Heart Beat, Shaw and Sons, London, 1925
 Blood, Heart, and Circulation Publication of American Association for Advancement of Science, No 13, Science Press, Washington, D C, 1940

- Henke, F and Lubarsch, O Handbuch der speziellen pathologischen Anatomie und Histologie, Julius Springer, Berlin, 1924
- A. Monckeberg, J G and Ribbert, Hugo
On the Heart
- B Jores, L
On Arteries
- C Benda, C
On Veins
- Ashman, R and Hull, E Essentials of Electrocardiography for the Student and Practitioner of Medicine, second edition, The Macmillan Co, New York, 1941
- Pardee, H Clinical Aspects of the Electrocardiogram including the Cardiac Arrhythmias, 4th edition Paul Hoeber, New York, 1941
- Baines, Arlie Electrocardiographic Patterns C C Thomas, Springfield, Ill, and Baltimore, Md, 1940
- Graybiel, A, and White, P D Electrocardiography in Practice, W B Saunders Co, Philadelphia, 1941
- Roesler, Hugo Clinical Roentgenology of the Cardiovascular System C C Thomas, Springfield, Ill and Baltimore, Md, 1937
- Roesler, Hugo Atlas of Roentgenology C C Thomas, Springfield, Ill and Baltimore, Md, 1940
- Laubry, Ch, et al Radiologie clinique du coeur et des gros Vaisseaux, Masson et Cie, Paris, 1939
- Lewis, Thomas Diseases of the Heart, 2nd edition The Macmillan Company, New York, 1937
- White, Paul D Heart Disease, 2nd edition The Macmillan Company, New York, 1937
- Levine, Samuel Clinical Heart Disease, 2nd edition, W B Saunders Co, 1940
- Stroud, William D Diagnosis and Treatment of Cardiovascular Disease, 2 volumes F A Davis Company, Philadelphia, Pa, 1940
- Herrmann, George R Synopsis of Diseases of the Heart and Arteries, 2nd edition C V Mosby Co, St Louis, 1941
- Levy, Robert Diseases of the Coronary Arteries and Pain The Macmillan Company, New York, N Y, 1936
- Fishberg, A M Heart Failure Lea & Febiger, Philadelphia, 1937
- Harrison, T R Failure of the Circulation, 2nd edition Williams and Wilkins Company, Baltimore, Md, 1939
- Homans, John Circulatory Diseases of the Extremities The Macmillan Company, New York, N Y, 1939
- Leaman, William G, Jr Management of the Cardiac Patient J B Lippincott Company, Philadelphia, 1940

GASTRO-INTESTINAL DISEASES

COURSE No 5

Liver Function

- Mann, F C The Liver and Medical Progress, J A M A, 117 1577 (Nov 8) 1941
- Bockus, H L, and Tumen, H J Jaundice, The Cyclopedia of Medicine, Surgery and Specialties, Philadelphia, F A Davis Co 8 168-205, 1939
- Ravdin, I S The Protection of the Liver from Injury, Surgery, 8 204-211 (Aug) 1940
- Epstein, E Z, and Greenspan, E D Clinical Significance of Cholesterol Partition of the Blood Plasma in Hepatic and Biliary Diseases, Arch Int Med 58 860, 1936

- Lehmhierr, E. R : The Value of the Icteric Index and Plasma Lipids in the Diagnosis of Jaundice *New Eng J Med* 211 487-492 (Sept 14) 1934
- Sperry W. M.: The Relationship Between Total and Free Cholesterol in Human Blood Serum *J Biol Chem* 114: 125-131 (May) 1936
- Block W. D., Buchanan M. S. and Freyberg R. H. Serum Lipids in Rheumatoid Arthritis and in Patients with Obstructive Jaundice, *Arch Int Med* 68: 18 (July) 1941
- Tumen H., and Bockus, H. L. The Clinical Significance of Serum Proteins in Hepatic Diseases *Am. J Med Sci* 193 788 (June) 1937
- Quick A. J. The Nature of the Bleeding in Jaundice, *J A M A* 110 1658 (May 14) 1938
- Stewart J. D.: Clinical Significance of Prothrombin Deficiency and Its Treatment *Ann Surg*, 114 907-918 (Nov.) 1941
- Rhoads J. E. Warren R., and Panzer, L. M. Experimental Hypoprothrombinemia, *Am. J Med Sci* 202 847-861 (Dec) 1941
- Rothman M. M. Meranze, D. R. and Meranze, T. Blood Phosphatase as an Aid in the Differential Diagnosis of Jaundice *Am J Med Sci* 192 526 (Oct) 1936
- Woodward H. Q. and Higinbotham, N. L. Serum and Tissue Phosphatase Determinations, *J A M A* 116 1621 (Apr 12) 1941.
- Shay, H. and Fieman P. The Galactose Tolerance Test in Jaundice *Ann Int. Med* 10. 1297 (Mar) 1937
- Tumen, H. J. and Piersol G. M. The Value of Alimentary Galactosuria in the Diagnosis of Jaundice *Ann Int Med* 12 311-329 (Sept) 1933
- Shay, H. and Fieman P. The Value of a Combined Study of the Newer Laboratory Tests in the Differential Diagnosis of Toxic and Obstructive Jaundice, Including Blood Phosphatase Cholesterol Partition Galactose Tolerance and Glucose Tolerance, *Am J Dig Dis* 5 597 (Nov) 1938
- Rosenberg D. N. Cephalin-Cholesterol Flocculation Test *Arch Surg* 43 231 (Aug) 1941
- Snell, A. M. and Magath T. B. The Use and Interpretation of Tests for Liver Function *J. A M A* 110 167 (Jan 15) 1938

Chronic Gastritis

- Monaghan J. F. Bockus, H. L. Kornblum, K. and Moffit, G. R. Gastric Secretory Behavior in Chronic Gastritis *Am J Dig Dis* 3 655 (Nov) 1936
- Schindler R. Gastroscopy Univ of Chicago Press, 1937
- Ansprenger A. and Kirklin B. R. Roentgenologic Aspects of Chronic Gastritis, *Am J Roentgenol and Rad. Ther* 38 533 1937
- Golden R. Antral Gastritis and Spasm *J. A M A* 109 1497, 1937.
- Johnson, T. A. Acute and Chronic Gastritis *Tice Practice of Medicine* W. F. Prior Co Inc Vol VII p 417-432
- Jones, C. M. Clinical Evaluation of Gastritis *Am J Dig Dis* 8 205 (June) 1941
- Tumen H. J. and Lieberthal M. M. Chronic Gastritis A Review of the Present Status. *New International Clinics* Philadelphia J. B. Lippincott Co, 1941, Vol 2, pp 263-291
- Swalm W. A. and Morrison, L. M. Gastroscopic and Histologic Studies of the Stomach with Gastric and Extragastric Diseases During Life and at Autopsy, *Am J Digest. Dis* 8 391-397 (Oct) 1941

Clinical Demonstrations

- Bockus, H. L., Shay H. Willard J. H. and Pessel, J. F. Comparison of Biliary Drainage and Cholecystography, Gallstone Diagnosis *J A M A* 96 311 (Jan 31) 1931

- Rousselot, L M, and Bauman, L Cholesterol Crystals and Calcium Biliubinate Granules Their Significance in Bile Obtained through the Duodenal Tube, *J. A. M. A* 100 254-256 (Jan 28) 1933
- Craig, C F, and Faust, E C Clinical Parasitology, Lea and Febiger, Philadelphia, 1940

Esophagus

- Tucker, Gabriel. Diseases of the Esophagus Diagnosis and Treatment. Esophagoscopic Observations, Proceedings of the Inter-State Postgraduate Medical Assembly of North America, October 1935, Detroit, Michigan
- Tucker, G, and Thigpen, F M Esophageal Diverticulum, with Report of 10 Cases of Pulsion Type Originating in Pharynx, Surgery, 2 188 (Aug) 1937.
- Tucker, Gabriel Cicatricial Stenosis of the Esophagus with Particular Reference to Treatment by Continuous String Retrograde Bouginage with the Author's Bougie (Report of twenty-five cases), Transactions of the 30th Annual Meeting of the American Laryn, Rhinol and Otol Society, 1924

Nutritional Deficiencies and Gastro-intestinal Disorders

- Elsom, K O, Lukens, F D W, Montgomery, E H, and Jonas, L Metabolic Disturbances in Experimental Human Vitamin B Deficiency, *J Clin Investigation*, 19 153 (Jan) 1940
- Elsom, K O, Lewy, F H, and Heublein, G W Clinical Studies of Experimental Human Vitamin B Complex Deficiency, *Am J M Sc* 200 757 (Dec) 1940
- Mackie, T T, and Pound, R E Changes in the Gastro-intestinal Tract in Deficiency States, *J A M A* 104 613, 1935
- Bennett, T I, Hunter, D, and Vaughan, J M Idiopathic Steatorrhea (Gee's Disease), A Nutritional Disturbance Associated with Tetany, Osteomalacia and Anemia, *Quart J Med* 1 603, 1932
- Thaysen, T E H Ten Cases of Idiopathic Steatorrhea, *Quart J Med* 4 359, 1935
- Snell, A M, and Camp, J O Chronic Idiopathic Steatorrhea Roentgenologic Observations, *Arch Int Med* 53 615, 1934
- Verzar, F, and McDougall, E J Absorption from the Intestine, London, Longmans, Green and Co 1936
- Golden, R The Small Intestine and Diarrhea, *Am J Roent* 36 892 (Dec) 1936
- Kirklin, B R, and Weber, H M Roentgenologic Diagnosis of Diseases of the Small Intestine, *Am J Dig Dis* 7 475 (Nov) 1940
- Golden, Ross Nutritional Disturbances of the Small Bowel, *Radiology* 36 262, (March) 1941

Functional Disorders of the Gastro-intestinal Tract

- Dunbar, F Emotions and Bodily Changes A Report of Some Recent Psychosomatic Studies, *Ann Int. Med* 14 839 (Nov) 1940
- McCullagh, E P, and Tupper, W R Anorexia Nervosa, *Ann Int Med* 14 817 (Nov) 1940
- White, B V, and Jones, C M Mucous Colitis A Delineation of the Syndrome with Certain Observations on its Mechanism and on the Role of Emotional Tension as a Precipitating Factor, *Ann Int Med* 14 854 (Nov) 1940
- Bockus, H L The Irritable Colon Diagnosis and Treatment, *Med Clinics No America*, July, 1937
- Gray, I, Harten, M, and Walzer, M Studies in Mucous Membrane Hypersensitivity, Allergic Reaction in Passively Sensitized Mucous Membranes of Ileum and Colon in Humans, *Ann Int Med* 13 2050 (May) 1940

Conn, J W The Spontaneous Hypoglycemias, J A M A 115 1669 (Nov 16) 1940

Regional Enteritis and Enterocolitis

Crohn, B B, Ginsburg, L, and Oppenheimer, G D Regional Ileitis, J A M A 99 1323 (Oct 15) 1932

Marshall, S F Regional Ileitis, New Eng J Med, 222 375 (Mar 7) 1940

Bockus, H L, Johnson, T A, and Lee, W E Appraisal of Results of Surgically Treated Chronic Regional Ileitis Lahey Birthday Vol, pp 53-83, 1940

Pancreatic Disorders

Johnson, T A, and Bockus, H L Diagnostic Significance of Determinations of Serum Lipase, Arch Int Med 66 62 (July) 1940

Dozzi, D L Urinary Amylase Its Estimation and Significance, Am Dig Dis 7 123 (Mar) 1940

Berk, J E Diagnosis of Carcinoma of the Pancreas, Arch Int Med 68 525 (Sept) 1941

Peptic Ulcer

Feigenbaum, J, and Howat, D The Relation Between Physical Constitution and the Incidence of Disease, J Clin Invest 13 121, 1934, Arch Int Med 55 445, 1935

Neches, H A Theory on the Formation of Peptic Ulcer, Am J Digest Dis 4 643 (Dec) 1937

Boles, R S, Riggs, H E, and Griffiths, J O The Role of the Circulation in the Production of Peptic Ulcer, Am J Digest Dis 6 632 (Nov) 1939

Sandweiss, D J, Saltzstein, H C, and Farbman, A A The Relation of Sex Hormones to Peptic Ulcer, Am J Digest Dis 6 6 (March) 1939

Vanderahe, A R Histopathologic Changes in the Nervous System in Cases of Peptic Ulcer, Arch Neur and Psychiatry 41 871 (May) 1939

Quigley, J P Enterogastrene, Significant Steps in Development of the Present Conceptions, Am J Digest Dis 8 363 (Oct) 1941

Gray, J S Present Status of Urogastrene, Am J Digest Dis 8 365 (Oct) 1941

Palmer, W L, and Nutter, P B A Further Study of the Role of Acid Gastric Juice in the Pathogenesis of Peptic Ulcer, Arch Int Med 65 499 (Mar) 1940

Cole, L G Anatomical Factors Predisposing to Corporic Ulcer, New Eng Jour Med 201 1081 (Nov 28) 1929

Palmer, W L Benign and Malignant Gastric Ulcers Their Relation and Clinical Differentiation, Ann Int Med 13 317 (Aug) 1939

Ravdin, I S, Stengel, A, Jr, and Prushankin, M The Control of Hypoproteinemia in Surgical Patients, J A M A 114 107 (Jan 13) 1940

Lahey, F H Diagnosis and Management of Gastrojejunal Ulcer and Gastrojejunal Colic Fistula, S Clin North America 20 767 (June) 1940

Jordan, S M End Results of Radical Surgery of the Gastro-intestinal Tract as Seen by the Gastro-enterologist, J A M A 116 586 (Feb 15) 1941

Jones, C M The Problem of Gastrectomy and the Anemias, Am J Digest Dis 7 502 (Nov) 1940

Miller, T G Management of Complications of Peptic Ulcer, New Eng J Med 224 401 (Mar 6) 1941

Nicholson, J T L, and Miller, T Grier The Prompt Feeding Program for Bleeding Gastric and Duodenal Ulcer, Am J Dig Dis 8 446 (Dec) 1941

Ravdin, I S, and Johnston, C G Some Observations on Perforated Gastric and Duodenal Ulcer, Am J Med Sci 200 275 (Aug) 1940

Achlorhydria

- Bockus, H L, Bank, J, and Willard, J H Achlorhydria with a Review of 210 Cases in Patients with Gastro-intestinal Complaints, *Am J Med Sci* 184 185 (Aug) 1932
- Davies, D T, and James, T G I *Lancet*, 2 899, 1930
- Dameshek, W Chronic Hypochromic Anemia, *Cyclopedia of Medicine, Surgery and Specialties*, Philadelphia, F A Davis Co 1939, Vol 2, p 736
- Heath, C W Anemia Due to Iron Deficiency, A Symposium on the Blood and Blood-forming Organs, University of Wisconsin Press, 1939, p 41
- Minot, G R Anemias of Nutritional Deficiency, A Symposium on the Blood and Blood-forming Organs, University of Wisconsin Press, 1939, p 52
- Meulengracht, E Some Etiological Factors in Pernicious Anemia, A Symposium on the Blood and Blood-forming Organs, University of Wisconsin Press, 1939, p 72

Miscellaneous

- Abbott, W O, and Johnston, C G Intubation Studies of the Human Small Intestine, *Surg, Gyn and Obstet* 66 691 (Apr) 1938
- Jones, C M Gastro-enterology, A Review of Literature from July 1940 to July 1941, *Arch Int Med* 68 763 (Oct) 1941
- Jones, C A A Clinical and Laboratory Study of Plasma Lipids in Obstructive Jaundice and Several Types of Hepatic Disease, *Amer Jr Dig Dis* 9 1-13, January, 1942

 ARTHRITIS AND RHEUMATIC DISEASES

COURSE No 7

- Hench, Philip S, Bauer, Walter, Dawson, M Henry, Hall, Francis, Holbrook, W Paul, Key, J Albert, and McEwen, Currier The Problem of Rheumatism and Arthritis, Review of American and English Literature for 1939
- Seventh Rheumatism Review, Part I, *Ann Int Med*, 14 1383, (Feb) 1941
- Part II, *Ann Int Med*, 14 1631, (March) 1941
- Review of American and English Literature for 1940
- Eighth Rheumatism Review, Part I, *Ann Int Med*, 15 1002, (Dec) 1941
- Part II, *Ann Int Med*, 16 , (Jan) 1942
- (Note The preceding reviews, First to Sixth inclusive, also appeared in the *Annals of Internal Medicine*, one review each year, from 1935 forward)

 PERIPHERAL VASCULAR DISEASES, INCLUDING HYPERTENSION

COURSE No 8

- 1 Ochsner, Alton and Mahorner, Howard Varicose Veins C V Mosby Co St Louis 1939
- 2 Herrmann, Louis G Passive Vascular Exercise J B Lippincott Co Philadelphia 1936
- 3 Samuels, Saul S The Diagnosis and Treatment of Diseases of the Peripheral Arteries Oxford University Press New York 1936
- 4 Brown, George E, Allen, E V and Mahorner, Howard Thrombo-angitis Obliterans W B Saunders Co Philadelphia 1928
- 5 Collens, William S and Wilansky, Nathan D Peripheral Vascular Diseases Charles C Thomas Springfield, Illinois 1939

- X6 Kvale, Walter F and Allen, E V The Rate of Circulation in the Arteries and Veins of Man *Am Heart J* 18 519-536, 546-556, 557-561 (Nov) 1939
- X7 Scupham, George W, deTakats, Geza, VanDellen, T R and Beck, W C Vascular Diseases, a Review of Some of the Recent Literature with a Critical Review of the Surgical Treatment *Arch Int Med* 64 590-655 (Sept) 1939
- X8 Wright, I S The Treatment of Arteriosclerosis Obliterans, Social Significance and Ultimate Objective *J A M A* 115 893-895 (Sept 14) 1940
- X9 Wright, I S Physical Therapy in Peripheral Vascular Disease *Arch Phys Therapy* 19 161-172 (Mar) 1938
- X10 Holman, Emile Clinical and Experimental Observations on Arteriovenous Fistulae *Ann Surg* 112 840-875 (Nov) 1940
- 11 Barker, N W Results of Treatment of Thrombo-angitis Obliterans by Foreign Protein *J A M A* 97 841-843 (Sept 19) 1931
- X12 Barker, N W General Classification of Diseases of Veins and Clinical Types of Thrombophlebitis *Proc Staff Meet, Mayo Clin* 9 191-194 (Mar 28) 1934
- X13 Barker, N W Diseases of the Veins *M Clin North America* 19 535-543 (Sept) 1935
- 14 Chew, E M, Allen, E V and Barker, N W Orthostatic Hypotension a Report of Six Cases and Review of the Literature *Northwest Med* 35 297-303 (Aug) 1936
- 15 Goldblatt, Harry Studies on Experimental Hypertension the Pathogenesis of Experimental Hypertension due to Renal Ischemia *Ann Int Med* 11 69-103 (July) 1937
- 16 Page, I H Newer Aspects of Experimental Hypertension American Association for the Advancement of Science Publication 13, pp 239-265
- 17 Weiss, Soma Recent Advances in the Treatment of Arterial Hypertension *Med Clin North America* 1343-1365 (Mar) 1936
- 18 Barker, M H The Use of Cyanates in the Treatment of Hypertension *Wisconsin M J* (Jan) 1937
- 19 Barker, M H The Blood Cyanates in Treatment of Hypertension *J A M A* 106 762-767 (Mar 7) 1936
- X20 Allen, E V and Adson, A W The Treatment of Hypertension, Medical versus Surgical *Ann Int Med* 14 288-307 (Aug) 1940
- 21 Adson, A W Surgical Treatment of Peripheral Vascular Diseases *Proc Interstate Post-Graduate Med Assoc of North America* 196-199, 1940
- 22 Craig, W McK and Smith, H L The Surgical Treatment of Hypersensitive Carotid Sinus Reflexes A report of thirteen cases *J Biology and Medicine* 11 415-422 (Mar) 1933
- X23 Craig, W McK Hypertension and Consideration of Its Surgical Treatment *Brit M J* 2 1215-1219 (Dec 23) 1939
- 24 MacLean, A R and Allen, E V Orthostatic Hypotension and Orthostatic Tachycardia Treatment with "Head-up" Bed *J A M A* 115 2162-2167 (Dec 21) 1940
- X25 Hines, E A Variability of the Blood Pressure *Virginia Med Monthly* 67 757-759 (Dec) 1940
- X26 Hines, E A The Significance of Vascular Hyper-reaction as Measured by the Cold-pressor Test *Am Heart J* 19 408-416 (Apr) 1940
- X27 Hines, E A and Barker, N W Arteriosclerosis Obliterans a Clinical and Pathologic Study *Am J M Sc* 200 717-730 (Dec) 1940
- X28 Keith, N M, Wagener, H P and Barker, N W Some Different Types of Essential Hypertension Their Course and Prognosis *Am J M Sc* 197 332-343 (Mar) 1939

- 29 Smith, L A and Allen E V Erythromelalgia (Erythromelalgia) of the Extremities, a Syndrome Characterized by Redness, Heat, and Pain *Am Heart J* 16 175-188 (Aug) 1938
 - 30 McKechnie, R E and Allen, E V Sudden Occlusion of the Arteries of the Extremities Study of 100 Cases of Embolism and Thrombosis *Surg, Gynec and Obst* 63 230-240 (Aug) 1936
 - 31 Allen, E V and Ghormley, R K Lymphedema of the Extremities Etiology, Classification, and Treatment, Report of 300 Cases *Arch Int Med* 54 606-624 (Oct) 1934
 - 32 Scott, R W Hypertension a Century After Bright *J A M A* 3 2460-2463 (Dec 31) 1938
 - 33 Wiggeis, C J Mechanisms of Peripheral Circulatory Failure *Ann Int Med* 15 178-189 (August) 1941
 - 34 Page, I H, and associates Reduction of Arterial Blood Pressure with Extracts of Kidney *Jour Exper Med*, 73 7-41 (January) 1941
- X—Checked in the Cumulative Index Medicus

GASTRO-INTESTINAL DISEASES

COURSE No 9

Books

Portis Diseases of the Digestive System
 Eusterman and Balfour Stomach and Duodenum
 Walters and Snell Diseases of the Gall Bladder and Biliary Tract
 Alvarez Nervous Indigestion
 Schindler Gastroscoy The Endoscopic Study of Gastric Pathology
 Berg, H H Roentgenuntersuchungen am innenrelief des vergauungskanal
 Livingston and Pack Prognosis of Gastric Carcinoma
 Bloomfield and Pollard Gastric Anacidity
 Rankin, Bargaen, and Buie The Colon, Rectum, and Anus
 Craig Amoebiasis and Amoebic Dysentery

Articles

Ivy, A C Some Recent Advances in the Physiology of the Alimentary Tract, *Am J Digest Dis* 8 361, 1941
 Jones, C M Medical Progress Treatment of Biliary Tract Disease, *New Eng J Med* 224 509, 1941
 Jones, C M Progress in Internal Medicine Gastro-enterology A Review of Literature from July, 1940, to July, 1941, *Arch Int Med* 68 763, 1941

INTERNAL MEDICINE

COURSE No 10

Blood

Bell Textbook of Pathology
 Maximow-Bloom Text Book of Histology
 Downey Handbook of Hematology
 Ewald, O Die leukamische Retikuloendotheliose *Deutsches Arch f klin Med* 142 222, 1923
 Clough, P W Monocytic Leukemia *Johns Hopkins Hospital Bulletin* 51 148, 1932
 Downey, Hal Monocytic Leukemia and Leukemic Reticuloendotheliosis *Handbook of Hematology* 1274-1329 Paul B Hoeber, New York 1938

The 1941 Yearbook of Pathology and Immunology, pages 499-513

Levine, Philip Am J Clin Path 11 898, 1941

Levine, Bunham, Katzin, and Vogel Am J Obs and Gynec 42 925, 1941

Watson, C J Hemolytic Jaundice, Etc Ann Int Med 12 1782, 1939

Castle, W B, and Minot, G R Pathological Physiology and Clinical Description of the Anemias Oxford Med pp 18, 23-117 1936

Ham, Thomas Hale, and Castle, William B Studies on Destruction of Red Blood Cells Relation of Increased Hypotonic Fragility and of Erythrostatics to the Mechanism of Hemolysis in Certain Anemias Reprinted from Proceedings of the American Philosophical Society 82 No 4, 1940

Rosenthal, N Hemorrhagic Diathesis In Downey's Handbook of Hematology Sect VIII Paul Hoeber, 1938

Liver and Biliary Tract

Martin, L Jaundice Internat Clinics 1 19, 1934

Weir, J F, and Parch, W J The Relationship of Pain to Jaundice Ann Int Med 4 1509, 1931

Bassett, A M, Althausen, T L, and Coltrin, G C A New Galactose Test for Differentiation of Obstructive from Parenchymatous Jaundice Am J Dig Dis 8 432, 1941

Watson, C J Diseases of the Gall Bladder and Biliary Tract In Cecil's Textbook of Medicine 5th Edition Saunders & Company 1940

Watson, C J Pyrrol Pigments In Downey's Handbook of Hematology v IV Paul Hoeber and Co 1938

Lord I W, and Andrus, W D Differentiation of Intrahepatic and Extra Hepatic Jaundice Response of Plasma Prothrombin to Intramuscular Injection of 2-Methyl, 1, 4 Naphtho Quinone, as Diagnostic Aid Arch Int Med 68 199, 1941

Patek, A J, and Post, J Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex J Clin Investig 20 481, 1941

Thompson, William P, Caughey, John L, Whipple, Allen O, and Rousselot, Louis M Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome) Reprinted from J Clin Investig 16 No 4 (July) 1937

Snell, Albert M Recent Advances in Treatment of Hepatic Disease Reprinted from Minnesota Medicine 23 551 (August) 1940

Rousselot, Louis M The Late Phase of Congestive Splenomegaly (Banti's Syndrome) with Hematemesis but without Cirrhosis of the Liver Reprinted from Surgery 8 No 1, 34-42 (July) 1940

White, Franklin W, Deutsch, Emmanuel, Maddock, Stephen The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester and Phospho-Lipid Tests in Diseases of the Liver Clinical Comparison of the Tests Reprinted from The American Journal of Digestive Diseases 7 No 1, 3-7 (January) 1940

White, Franklin W, Deutsch, Emmanuel, and Maddock, Stephen The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester and Phospho-Lipid Tests in Diseases of the Liver The Results of the Tests Reprinted from The American Journal of Digestive Diseases 6 No 9, 603-610 (November) 1939

Watson, C J Regurgitation Jaundice J A M A 114 2427, 1940

White, Franklin W The Galactose Tolerance and Urobilinogen Tests in the Differential Diagnosis of Painless Jaundice Reprinted from the American Journal of Digestive Diseases and Nutrition 4 No 5 (July) 315-325

Metabolism and Endocrinology

- Means, J H The Thyroid and Its Diseases Chapt VIII, X, XIV J B Lippincott Co, Phila, 1937
- Althausen, T L The Disturbance of Carbohydrate Metabolism in Hyperthyroidism J A M A 115 101, 1940
- Althausen, T L, Lockhart, J C, and Soley, M H A New Diagnostic Test (Galactose) for Thyroid Disease Am J Med Sci 199 342, 1940
- Bauer, W, and Camp, J D Malacic Diseases of Bone In Nelson's New Looseleaf Surgery Thomas Nelson & Sons, New York, 3 175N-177C, 1937
- Camp, J D Roentgenologic Changes in Malacic Diseases of Bone Radiology 26 399-408 (April) 1936
- Jaffe, H L Resorption of Bone, a Consideration of the Underlying Processes Particularly in Pathologic Conditions Arch Surgery 20 355-385 (March) 1930
- Hunter, Donald Studies in Calcium and Phosphorus Metabolism in Generalized Diseases of Bones Proc Roy Soc Med 28 1619-1638 (October) 1935
- Eighth Rheumatism Review Annals of Internal Medicine December, 1941
- Hench, P S The Diagnosis and Treatment of Gout and Gouty Arthritis Journal A M A February 8, 1941
- Ludwig, A O, Bennett, G A, and Bauer, Walter A Rare Manifestation of Gout, Widespread Ankylosis Simulating Rheumatoid Arthritis Annals of Internal Medicine January, 1938
- McQuarrie, Irvine, Johnson, R M, and Ziegler, M R Plasma Electrolyte Disturbance in Patient with Hypercorticotadrenal Syndrome Contrasted with that Found in Addison's Disease Endocrinology 21 762, 1937
- Wilson, D M, Power, M H, and Kepler, E J Alkalosis and Low Plasma Potassium in a Case of Cushing's Syndrome A Metabolic Study J Clinical Investigation 19 701, 1940
- Albright, F, Parson, W, and Bloomberg, E Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis Results of Treatment with Testosterone Propionate J Clin Investigation 1 375, 1941

Diseases of Gastro-intestinal Tract

- Cave, Henry W, and Thompson, James E Mortality Factors in the Surgical Treatment of Ulcerative Colitis Annals of Surgery 114 46 (July) 1941
- Livingston, Edward M, and Pack, George T End Results in Treatment of Gastric Cancer
- Allen, Arthur W, and Welch, Claude E Gastric Ulcer The Significance of This Diagnosis and Its Relationship to Cancer Annals of Surgery 114 498-509 (October) 1941
- Parsons, Langdon, and Welch The Curability of Carcinoma of the Stomach Surgery 6 327-338, 1939
- Gray, H K Carcinoma of Stomach Encouraging Results of Surgical Treatment Proceedings of Interstate Postgraduate Medical Assembly of North America (1940), 139-141, 1941
- Gray, H K, Walters, Waltman, and Priestley, J T Report of Surgery of the Stomach and Duodenum for 1940 Proceedings of the Staff Meetings of the Mayo Clinic 16 721-736 (November 12) 1941
- Fansler, W A The Origin of Polypi of the Large Bowel with Especial Reference to Adenoma Preliminary Report J A M A 95 1969-1970, 1930
- Kennedy, R L J, and Weber, H M Polyposis of the Colon in Children Am J Dis Child 42 69-76, 1931

- Schmieden, V, and Westhues, H Zur Klinik und Pathologie der Dickdampolypen und deren Klinischen und Pathologisch-anatomischen Beziehungen zum Dickdarmkarzinom *Deutsche Ztschr f Chir* 202 1-124, 1927
- Wesson, H R, and Bargaen, J A Classification of Polyps of the Large Intestine *Proc Staff Meet Mayo Clinic* 9 789-794, 1934
- Bargaen, J Arnold Important Newer Concepts Concerning Cancer of the Intestines and Their Bearing on Management *West Va Med J* 37 No 10 (October) 1941
- Thewlis, M The Care of the Aged (geriatrics) Mosby (St Louis) 1941
- Boas, Ernest P Treatment of the Patient Past Fifty Year Book Publ Chicago 1941
- McLester, J S Borderline States of Nutritive Failure *J A M A* 112 2110-2114 (May 27) 1939
- Schindler, R Early Diagnosis of Cancer of Stomach Reprint 1939 from Journal National Cancer Institute 1 No 4, p 451 (February) 1941 Also in *J A M A* 115 1693 (November 16) 1940
- Carey, J B Gastroscopic Observation of Postoperative Stomach *Surg, Gynec and Obst* 65 447 (October) 1937
- Moersch, H J, and Walters, Waltman Gastroscopic Observation of Postoperative Stomach *Surg, Gynec and Obst* 71 129 (August) 1940
- Carey, J B Gastroscopic Observation in Chronic Gastritis *Am J Dig Dis* 7 160 (April) 1940
- Carey, J B Observations in Achlorhydria *Am J Dig Dis* (November) 1941
- Schloss, J, Ettinger, A, and Pratt, J Diagnosis of Diseases of Stomach by Gastroscopic and X-ray Relief Studies *Am J Med Sc* 193 171 (February) 1937
- Templeton, R E, and Schindler, R Diagnosis of Diseases of Stomach by Gastroscopic and X-ray Relief Studies *Am J Roent and Rad Therap* 41 354 (March) 1939
- Eusterman, G B Peptic Ulcer Medical Management *Minnesota Medicine* 20 765-769 (December) 1937
- Eusterman-Balfour Text The Stomach and Duodenum Medical Treatment of Duodenal Ulcer Chapter 13, pp 275-294 Medical Treatment of Gastric Ulcer Chapter 28, pp 457-462
- Eusterman, G B Carcinomatous Gastric Ulcer, Misleading Results of Medical Therapy *J A M A* 118 1 (January 3) 1942

Cardiovascular System

- Clawson, B J Rheumatic Heart Disease *American Heart Journal* 20 454, 1940
- Clawson, B J Incidence of Types of Heart Disease Among 30,265 Autopsies with Special Reference to Age and Sex *American Heart Journal* 22 607, 1941
- Clawson, B J Syphilitic Heart Disease *Syphilitic and Cutaneous Review* 45 4 1941
- Brown, James W Congenital Heart Disease John Bale Medical Publications Ltd, 1939
- Abbott, M E Atlas of Congenital Heart Disease 1936
- White, P D Congenital Heart Disease Heart Disease
- Peters, H C, and Visscher, M B The Energy Metabolism of the Heart in Failure and the Influence of Drugs upon It *American Heart Journal* 11 273, 1936
- Visscher, M B The Energy Transformation by the Heart and the Mechanism of Experimental Cardiac Failure Pub No 13, American Association for the Advancement of Science, pp 176-183
- Harrison, Tinsley The Failure of the Circulation Williams and Wilkins Baltimore

- Loeb, Robert F Plasma Proteins in Health and Disease Reprinted from New England Journal of Medicine 224 980-987, 1941
- Page, Irvine H Newer Aspects of Experimental Hypertension Reprinted from Publication No 13 of American Association for the Advancement of Science, pp 239-265
- Samuels, Saul S The Diagnosis and Treatment of Diseases of the Peripheral Arteries Oxford University Press New York 1936
- Brown, George E, Allen, E V and Mahoiner, Howard Thrombo-angitis Obliterans W B Saunders Co Philadelphia 1928
- Collens, William S, and Wilensky, Nathan D Peripheral Vascular Diseases Charles C Thomas Springfield, Illinois 1939

Infectious Diseases

- Spink, W W The Pathogenesis and Treatment of Staphylococcal Infections The New International Clinics 4 236 (December) 1941
- Spink, W W, Hansen, A E, and Paine, J R Staphylococcic Bacteremia Treatment with Sulfapyridine and Sulfathiazole Arch Int Med 67 25, 1941
- Hoyt, W A, Davis, A E, and Van Buren, G Acute Hematogenous Staphylococcic Osteomyelitis J A M A 117 2043 (December 13) 1941
- Kiefer, C S Streptococcal Diseases New Eng J Med 220 109 (January 19) 1939
- Kiefer, C S, Ingelfinger, F J, and Spink, W W Significance of Hemolytic Streptococcic Bacteremia Arch Int Med 60 1084 (December) 1937
- Bliss, E A, Long, P H, and Feinstone, W H The Differentiation of Streptococci and Its Relation to Sulfanilamide Therapy South Med Jr 31 303 (March) 1938
- Reimann, H A, and Havens, W P An Epidemic Disease of the Respiratory Tract Arch Int Med 65 138 (January) 1940
- Ellis, R V, and McKinlay, C A Allergic Pneumonia Jr Lab and Clinical Medicine 26 1427 (June) 1941
- Spink, W W Sulfonamide Therapy Year Book Publishers, Inc, Chicago 1941
- Hitchens, A P, and Campbell, E P Communicable Diseases and Military Medicine Medical Clinics of North America 25 1589 (November) 1941
- Top, F H Handbook of Communicable Diseases The C V Mosby Company, St Louis 1941
- Cecil, Russell L The Control of Respiratory Infections Preventive Medicine, New York Academy of Medicine 9 p 64 (June) 1939
- Dochez, H R, Mills, Katherine C, and Kneeland, Yale, J Filterable Viruses in Infections of the Upper Respiratory Tract J A M A 110 p 127 (January 15) 1938
- Diehl, H S, Baker, A B, and Cowan, D W Cold Vaccines An Examination Based on a Controlled Study J A M A 111 p 1168 (September 24) 1938
- Sherman, J B Prophylaxis of the Common Cold British Medical Journal 2 p 903 (October 29) 1938
- Diehl, H S Medicinal Treatment of the Common Cold J A M A 101 p 2042 (December 23) 1933
- Spink, W W, and Hoffbauer, F W Brucellosis (Undulant Fever) A Brief Review with Case Analysis Reprinted from The Journal-Lancet LXI No 1, 13 (January) 1941
- Simpson, Walter M The Diagnosis and Management of Brucellosis Reprinted from Ann Int Med 15 No 3 (September) 1941

TUBERCULOSIS

COURSE No 11

Monographs

- Alexander, John The Collapse Therapy of Pulmonary Tuberculosis Thomas, Springfield, Illinois 1937
 Chapter by Max Pinner on "Physiological Principles of Collapse Therapy and Pathology of Pulmonary Collapse"
 Chapters by John B Barnwell on "Pneumothorax"
 Tuberculosis and Leprosy Symposium Series Amer Assoc Adv Science, 1938
 Terplan, K Anatomical Studies on Human Tuberculosis Suppl Amer Rev Tuberc 42 1 (Aug) 1940
 Lurie, M B Heredity, Constitution and Tuberculosis Suppl Amer Rev Tuberc 44 1 (Sept) 1941
 Sweany, H C Age Morphology of Primary Tubercles Published by C C Thomas, Springfield, Illinois 1941

Tuberculosis of Trachea and Bronchi

- Barnwell, J B, et al Ulcerative Tuberculous Tracheobronchitis Amer Rev Tuberc 36 8 (July) 1937
 Bugher, J C, et al Tuberculous Tracheobronchitis Its Pathogenesis Amer J Med Sc 193 515 (April) 1937
 Ornstein, G G, and Epstein, I G Tuberculosis of the Major Bronchi, etc Quart Bull Sea View Hosp 3 109 (Jan) 1938
 Riggins, H McL Tracheobronchial Tuberculosis, etc Trans 35th Annual Meeting Nat Tuberc Assoc, 1939
 Myerson, M C Tuberculosis of the Trachea and Bronchi J A M A 116 1611 (April 12) 1941

Pleuropulmonary Fistula

- Matsuzawa, D The Behaviour of Pneumothorax Gases in the Early Period of Artificial Pneumothorax Quart Bull Sea View Hosp 2 363, 1937
 Matsuzawa, D The Diagnosis of Pleuro-Pulmonary Fistula by Pneumothorax Air Analysis Quart Bull Sea View Hosp 4 286 (April) 1939
 Coryllos, P, and Welkind, A The Diagnosis of "Silent" Broncho-Pleural Fistula by Pleural Gas Analysis Quart Bull Sea View Hosp 4 377 (July) 1939
 Matsuzawa, D The Effect of Pneumothorax Pleuritis and Effusions Upon the Behavior of Pneumothorax Cases Quart Bull Sea View Hosp 5 40 (Oct) 1939
 Matsuzawa, D A Gas Sampling Tube with a Manometric Attachment for the Study of Pneumothorax Gases Quart Bull Sea View Hosp 5 186 (Jan) 1940
 Matsuzawa, D Diagnosis of Broncho-Pleural Fistula in Tuberculous Empyema Quart Bull Sea View Hosp 6 50 (Oct) 1940
 Welkind, A and Herman, M Rapid Re-Expansion of Lungs, Pleural Lavage with Oxygen Quart Bull Sea View Hosp 4 153 (Jan) 1939

Gastric Lavage, Monaldi Suction, Pneumo-peritoneum, etc

- Kayne, G G, Pagel, W, and O'Shaughnessy, M Pulmonary Tuberculosis Oxford University Press, 1939
 Chapters on Allergy, Immunity and Pathogenesis
 Miller, J A, and Wallgren, A Pulmonary Tuberculosis in Adults and Children N Y Nelson 1939
 Rich, A R, and McCordock, H A An Inquiry Concerning the Role of Allergy, Immunity and Other Factors of Importance in the Pathogenesis of Human Tuberculosis Bull J H Hosp 44 273, 1929

- Millet, J A Haematogenous Pulmonary Tuberculosis *Amer Rev Tuberc* 29 489, 1934
- Roper, W H, and Oldway, W H Gastric Lavage in Adults with Pulmonary Tuberculosis *Amer Rev Tuberc* 43 543, 1941
- Mishulow, L, Keieszturi, C, and Hauptman The Demonstration of Tubercle Bacilli in the Sputum, Faeces and Stomach Contents of Tuberculous Children *Amer Rev Tuberc* 29 471, 1934
- Banyai, Andrew L Therapeutic Pneumo-peritoneum *Amer Rev Tuberc* 29 603, 1934
- Salkin, David Pneumo-peritoneum in Intestinal Tuberculosis *Amer Rev Tuberc* 33 435, 1936
- Brown, L, and Sampson, H L Intestinal Tuberculosis *Lea and Febiger* 1930
- Trimble, H G, and Wardrip, B H Pneumo-peritoneum in Treatment of Pulmonary Tuberculosis *Amer Rev Tuberc* 36 111, 1937
- Goldman, A, Biunn, H, and Ackerman, L Tuberculous Cavities Observations on Trans-pleural Decompression *Amer Rev Tuberc* 43 151, 1931
- Guggenheim, A, and Finkelstein, M Continuous Transthoracic Aspiration of Pulmonary Cavities *Rky Mt Med J* 38 45, 1941
- Eloesser, L Blocked Cavities in Pulmonary Tuberculosis *J Thor Surg* 7 1, 1937
- Kupka, E, and Wells, R Technique of Cavity Aspiration (Monaldi), *Amer Rev Tuberc* 42 401, 1940
- Kupka, E, and Bennett, E S Monaldi's Suction Aspiration of Tuberculous Cavities *Amer Rev Tuberc* 42 614, 1940

Silicosis Bibliography

- First, Second, Third and Fourth Saranac Laboratory Symposia on Silicosis Edited by B E Kuechle, Wausaw, Wisconsin 1934, 1935, 1937 and 1939
- Tuberculosis in Industry, 1940 The National Tuberculosis Association, 1790 Broadway, New York City
- National Silicosis Conference, Bulletin No 21 Parts 1, 2, 3, and 4 1938 U S Dept of Labor, Washington, D C
- Teleky, R Pneumoconiosis 1938 Supplements to the encyclopaedia entitled, "Occupation and Health" The International Labour Office, 734 Jackson Place, Washington, D C
- Middleton, E L Silicosis 1938 Supplements to the encyclopaedia entitled "Occupation and Health" The International Labour Office, 734 Jackson Place, Washington, D C
- Amor, A J X-ray Atlas of Silicosis Williams and Wilkins Co, Baltimore, Md, 1941

Journals

American Review of Tuberculosis
Quarterly Bulletin of the Sea View Hospital

Excellent reviews on tuberculosis and other acute chronic pulmonary disorders may be found in review articles in the following journals

American Journal of Medical Science
Archives of Internal Medicine
New England Journal of Medicine

ANNOUNCEMENTS

Charles H Swift, chairman of the board of directors of Swift & Company, has announced the establishment of a series of fellowships for research in nutrition The

fellowships are intended to aid the federal government in its long-range national nutrition program

The fellowships provide for special research to be undertaken in laboratories of universities and medical schools with funds which the company has set aside as grants in aid, beginning November 1, 1941. The fellowships will be for one year but may be renewed where the project warrants it. Any fundamental study of the nutritive properties of foods or the application of such information to improvement of the American diet and health will be eligible for consideration for a grant

The Medical and Surgical Relief Committee of America, 420 Lexington Avenue, New York, N. Y., has as its objective to make up, through the cooperation of a nationwide committee of some 350 prominent physicians and surgeons, shortages in surgical and medical supplies in America. On December 15, 1941, at the request of Mayor Angelo J. Rossi, of San Francisco, two complete medical catastrophe units were shipped to the West Coast—the shipment being made in keeping with the Committee's new policy of concentrating future activities on furnishing aid to American hospitals and other organizations where they are required for emergency use. Arrangements are now under way to send similar first-aid medical and surgical units to hospitals in the States of New York, South Carolina, Maine and Vermont in response to urgent requests

The next annual meeting of the Mississippi Valley Medical Society will be held September 30 to October 2, 1942, at Quincy, Ill.

The 71st Annual Meeting of the American Public Health Association will be held in St. Louis, Mo., October 26-30, 1942

The biennial meeting of the Rocky Mountain Medical Conference will be held in Albuquerque, N. M., May 18-20, 1943

The Dallas Southern Clinical Society will hold its 14th Annual Spring Clinical Conference March 23-26, 1942. Among the honor guests at this meeting will be Dr. Edward G. Billings, F. A. C. P., Associate Professor of Psychiatry, University of Colorado School of Medicine, and Director of Psychiatric Liaison Department, Colorado General and Colorado Psychiatric Hospitals, Denver; Dr. Lewis M. Hurxthal, F. A. C. P., Physician-in-Charge, Department of Internal Medicine, Lahey Clinic, Boston, Mass.; and Dr. Andrew C. Ivy, F. A. C. P., Nathan Smith Davis Professor of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Ill.

Dr. Harold Swanberg, F. A. C. P., Quincy, Ill., who is Secretary of the Mississippi Valley Medical Society, has announced that the Society offers annually a cash prize of \$100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society at Quincy, Ill., September 30-October 2, 1942, the Society reserving the exclusive right to first publish the essay in its official publication, the *Mississippi Valley Medical Journal*. Contributions shall not exceed 5000 words, be typewritten in English in manuscript form, submitted in five copies and be received not later than May 1, 1942.

OBITUARIES

CAPTAIN JESSE BUNDREN HELM

Captain Jesse Bundren Helm, Medical Corps, U S Navy, retired, died in the Garfield Hospital, Washington, D C , November 26, 1941, of hypertensive heart disease, at the age of 56

Captain Helm was born in Tennessee in 1885 He attended the Edwards Seminary at White Pine, Tenn , and received his medical degree in 1911 from the University of Louisville School of Medicine He entered the Naval service July 20, 1913, and served in various positions until August 1, 1940, when he retired for disability incurred in the line of duty He was a member of the Southern Medical Association and Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1936

DR JOHN ARTHUR ALVAREZ

Dr John Arthur Alvarez was born August 13, 1905, at Fort Smith, Ark His academic education was received at the University of Arkansas, at Fayetteville, from which he was graduated with the degree of B A in 1926 He graduated from Tulane University of Louisiana School of Medicine, New Orleans, in 1930, after which he served a two-year internship at the Charity Hospital in that city He served as resident physician at St Joseph's Infirmary in Houston, Tex , in 1932, and then spent two years in the Department of Medicine of the Harvard Medical School and the Peter Bent Brigham Hospital, Boston, Mass Dr Alvarez entered the practice of Internal Medicine in Houston, in 1934, and rapidly became one of the leaders in his chosen profession He was a member of the Staff of the Medical Clinic of the Hermann Hospital, and an Associate in Medicine at St Joseph's Infirmary in Houston He was a member of the Harris County and Texas State Medical Societies, American Medical Association and American Heart Association He was a Diplomat of the National Board of Medical Examiners and of the American Board of Internal Medicine, and since 1940 had been a Fellow of the American College of Physicians

Dr Alvarez died on October 19, 1941, as a result of a fibrosarcoma of the chest wall with lung metastasis, after an illness of several months During these months Dr Alvarez persisted in the pursuit of his usual duties and his fortitude and resignation were a support to his family and an object lesson to his colleagues He is survived by his wife, his mother, and two sons

The medical profession of Houston and all Texas has lost a most capable physician and a sincere friend

M D LEVY, M D , F A C P ,
Governor for Texas

DR MARK TAD MORGAN

Dr Mark Tad Morgan (Associate), Dayton, Ohio, died October 8, 1941, at Middletown, Ohio. He was born May 7, 1902, in Middletown, Ohio, and received both his pre-medical and medical training at Ohio State University College of Medicine, receiving his M.D. degree in 1929. He entered the Medical Corps of the U.S. Army and served at various stations in this country and in Hawaii until August 31, 1940, when he retired for physical disability. He had attained the rank of Captain.

From December, 1940, until the time of his death he was associated in practice with Dr. Warren C. Breidenbach, F.A.C.P., Dayton, Ohio. He was Junior Chest Consultant to the Miami Valley Hospital, a member of the staff (Diseases of the Chest), Good Samaritan Hospital, and Assistant to the Director, Stillwater Sanatorium.

From both a medical and personal standpoint Dr. Morgan was outstanding, and his death was a deep blow to those associated with him.

DR IRA A. DARLING

Dr. Ira A. Darling died suddenly at 9:30 p.m., October 10, 1941, at the Torrance State Hospital, Torrance, Pa., where he had been superintendent since 1940. The immediate cause of death was coronary thrombosis.

Dr. Darling was born on March 9, 1888, at Aulcott, Vermont. He was left an orphan at an early age and moved to Meredith, New Hampshire, where he lived until he was ready to begin his pre-medical education, which was obtained at the Tilton Seminary, Tilton, New Hampshire. He entered the University of Vermont Medical School in 1907 and graduated in 1911. After a year's internship at the Lynn General Hospital he joined the medical staff at the Warren State Hospital, Warren, Pa., where he served as assistant physician and assistant superintendent under that outstanding neuropsychiatric administrator, Dr. Harry Mitchell.

Dr. Mitchell and Dr. Darling early recognized that the sound approach to neuropsychiatry was by means of a thorough physical as well as mental survey. Hence, they established at the Warren State Hospital a modern, well-equipped laboratory under the direction of a competent pathologist so that their patients could have the benefit of thorough scientific study. They also recognized the value of physical and occupational therapy and recreation in the restoration of their patients to as near a normal state of health as possible.

When Dr. Mitchell died in 1933, it was but natural that the board of directors should appoint Dr. Darling as superintendent. He continued as a most efficient administrator of the hospital until 1936 when a change in the state administration supplanted the boards of directors and superintendents with its own appointees for political and patronage reasons. It will indeed

be a fortunate day when the administrators of our state and municipal institutions of health are career men instead of political appointees

Dr Darling with his administrative experience, professional attainments and character easily won through civil service competitive examinations the appointment of superintendent of the Springfield State Hospital of Sykesville, Maryland, where he served with ability and distinction until 1940

In the meantime, there had been another change of administration in Pennsylvania, and he was called back to be superintendent of the Torrance State Hospital during a period of reconstruction and reorganization. While he was at Torrance less than two years, his associates there acclaim his ability as an organizer and administrator

Dr Darling was always a loyal and public spirited citizen. During the first world war, he was commissioned a First Lieutenant in the Medical Reserve Corps on December 28, 1917. He served with the American Expeditionary Force in France, partly with Base Hospital 89 and partly with the 138th Field Artillery. He was discharged from service in January, 1919, and resumed his duties at the Warren State Hospital. In the present emergency he was appointed by the Governor as consultant in neuropsychiatry for Pennsylvania Local Draft Board, Area No 8

At the time of his death, Dr Darling was a member of his county and state medical societies, of the Pittsburgh Neuropsychiatric Society, a Fellow of the American Medical Association, a Fellow of the American Psychiatric Association, a Fellow of the American College of Physicians, a Diplomat of the American Board of Psychiatry and Neurology, and a member of the Executive Committee of the Mental Hygiene Division Public Charities Association of Pennsylvania

Dr Darling is survived by his wife, Mrs Jennie McGill Darling, and his daughter, Miss Ella Darling, both residing at Williamsport, Pa

FREDERICK B UTLEY, M D , F A C P ,
Pittsburgh, Pa

LIEUT -COL GERALD ROSS BURNS

Dr Gerald Ross Burns died on November 16, 1941, a few days after he had undergone an emergency operation. He became ill while on duty at Debert, N S, where he was serving with His Majesty's Army as officer in charge of medicine, No 7 Canadian General Hospital

Though only about 40 years of age, Dr Burns held an enviable record in the field of medicine. He also took an active part in community affairs and other varied interests, and there are many institutions in Halifax that will mourn the passing of a true benefactor who gave much of his time, skill, and substance to charitable works

Surviving Dr Burns are his wife and two small children, his mother, two brothers, Right Rev W J Burns and Rev Dr John E Burns, and two sisters, Miss Eileen and Miss Eveleen

Dr Burns received his B A degree from St Marys College, Halifax, and his medical degrees from Dalhousie University. Following graduation, he was Assistant Superintendent of the Nova Scotia Sanatorium and later took a postgraduate course at the University of Pennsylvania. For the past ten years he acquitted himself honorably and well as a specialist in internal medicine, as Assistant Professor of Medicine at Dalhousie, and in many other important medical posts at Halifax, N S. He entered upon his army duties at the outbreak of war and gave all his time and energy to war work, in which his achievements were notable, and only his untimely death prevented him from serving his country overseas. He had been a fellow of the American College of Physicians since 1938.

Patriot, physician and teacher he was buried on November 16, surrounded as a Christian medical officer should be by members of the clergy, army, medical profession, medical students, former patients and friends, and with the last impressive rites of his church and the full military honors of the army of His Majesty the King, in whose uniform he answered the call to higher and fuller service.

J W MACINTOSH, M D , F A C P ,
Halifax, N S

COLONEL M A DAILEY

Dr Michael Andrew Dailey, Colonel, Medical Corps, U S Army, Surgeon Third Corps Area at Baltimore was fatally injured on October 27, 1941, when the automobile in which he was returning to Baltimore from Fort Meade, Maryland, was struck by an express train at Jessup station. Lieut Colonel Howard E Ashbury of the Army Medical Reserve, formerly Surgeon of the 4th Infantry Md N G , who was riding with Colonel Dailey was seriously injured.

Colonel Dailey was born on October 31, 1882, in North Easton, Mass. He was graduated from Dartmouth College in 1904 and from the Harvard Medical School in 1907, following which he served an internship in the Boston City Hospital. He was commissioned in the medical reserve corps of the Army in September 1911 and sent to the Army Medical School in Washington. Following graduation here he was commissioned in the regular corps on May 12, 1912, and ordered to Fort Sheridan, Illinois. Following a tour on the Mexican border at Fort Bliss, Texas (1913-14) he served two years in the Philippine Islands (1914-16). The World War found him in Fort Yellowstone, Wyoming, from which station he was ordered in August 1917 to New York City to take command of Base Hospital No 3 which was being organized at the Mount Sinai Hospital. In February the unit sailed for Europe and in May was operating at Vauclaire in the Department of Dordogne. He commanded this unit until October 1918. Later he was on hospital duty at Rennes, Ill-et-Vilaine. Returning to the United States in November 1919, he served for four years in posts in Texas and then was

transferred in December 1923 to the post of assistant to the Surgeon, Sixth Corps Area in Chicago. Always a keen student of internal medicine, he was detailed in December 1927 to Beaumont General Hospital as head of the medical service. In 1932 he was transferred to a similar position in the Walter Reed Hospital in Washington. A recent duty was the command of Gorgas Hospital at Ancon in the Canal Zone, from which service he returned in August 1941, taking over the place in the Corps Area Headquarters at Baltimore.

Colonel Dailey was one of the Army's notable specialists in internal medicine. His preparation for this work included a course at the Mayo Clinic. He was a fellow of the American College of Physicians and a diplomat of the American Board of Internal Medicine.

Colonel Dailey was married to Joann Margaret O'Brien, who with two sons and a daughter, survives him.

A large funeral cortege accompanied the remains from Baltimore to the Memorial Chapel at the Army Medical Center on October 30, where services were conducted by Chaplain Edward J. McTague of Walter Reed Hospital. Interment was in Arlington National Cemetery.

HISTORY OF PIONEER MEDICAL PRACTICE IN ST. PAUL*

By J M ARMSTRONG

IN the year 1847, Dr John Jay Dewey established himself at Saint Paul's Landing, now known as Saint Paul. Dr Dewey was a younger brother of the Governor of Wisconsin Territory and as Wisconsin was about to become a state, it was surmised that a new territory would be set up to the west, and that the capitol of the new territory would be a desirable place to settle. This we believe was the reason that influenced Dewey to come here.

At that time our population numbered about forty. Dr Dewey was a man of 25, had graduated from the Albany Medical College in March of that year, and remained here until his death in 1891.

When Minnesota Territory was established in 1849 with Saint Paul as its capitol, the town took on a rapid growth, there being about 300 inhabitants by the end of the year, and the number of physicians increased to six. Dr Thomas R. Potts became the first president of the Trustees of the town, and Dr David Day, Register of Deeds. Both these men were graduates of the University of Pennsylvania and both resided here the rest of their lives.

From this time on the town increased rapidly in population and not a few medical men made a trial of the practice of their professions here. Many of them remained but a short time, moving to other parts of the territory as settlement progressed.

In 1853 the first medical society in the territory was organized in Saint Paul, called "The Minnesota Medical Society." At that time there were about 20 medical men in the territory, and 13 of them responded to the call of the organizers. This society lived until 1857, when the last annual meeting was held in St. Ansbury, now part of Minneapolis. The financial panic of that year undoubtedly was the cause of its demise.

In 1850, Saint Paul had a population of 10,279, so one can see that growth was considerable. However, fur trading, the exportation of pine lumber and cranberries were the only industries.

In the year 1853, the cornerstone of our first hospital, and the first in the territory, was laid, but it did not open for patients until 1855. In 1854 and 1855 our city was invaded by an epidemic of Asiatic cholera which took its toll of both immigrants and residents, and put a severe test on the town.

In 1857 the predecessor of St. Luke's Hospital was established. It was not until many years later that other hospitals which now number 16 were established. At present these hospitals can care for 2,863 patients, and have 261 bassinets.

* The American College of Physicians will hold its Twenty-Sixth Annual Session in St. Paul, April 20-24, 1942.

In 1860 the Saint Paul Academy of Medicine and Surgery, our first local medical society, was formed. It was a most successful organization. A medical library was established, a laboratory put in operation, and a microscope and an electrical machine purchased. Some instruction to medical students was also given by its members in its halls. Unfortunately for this society, the Civil War interfered with its functions as all its members went into the army. When the war was over many new practitioners had settled in Saint Paul, and it was thought that since the members of the Academy could not take in the newcomers without sacrificing their funds, and since all had to recoup their fortunes, it would be wisest to disband. The lot that had been purchased for a home was sold, the books in the library returned to the donors, and the laboratory apparatus disposed of.

Informal medical meetings were held here until our Ramsey County Medical Society was organized in 1870, a year later than our present State Association. Since then our Society has had a prosperous career and many local and special medical societies have been organized.

Medical journalism and medical teaching started in Minnesota this same year, 1870, with the establishment of the Northwestern Medical and Surgical Journals, and the opening of the Saint Paul Medical College in Saint Paul by Dr. Alexander J. Stone. The journal, a quarterly, lasted four years and the Medical School until 1888 when the medical department of the University of Minnesota was established in Minneapolis with practically the entire teaching staff of the Saint Paul School on the faculty.

Since 1870 Saint Paul has been well known as a medical center, and many eminent physicians have practiced their profession here. The Medical Journal now known as the Journal-Lancet, was established in Saint Paul by Dr. Stone in 1881, but is now published in Minneapolis.

In 1899 the Saint Paul Medical Journal was started by the Ramsey County Medical Society and continued until 1917 when "Minnesota Medicine," the organ of the State Medical Association, was established, the Saint Paul Journal agreeing to disband its publication to protect the new journal.

The Ramsey County Medical Society has, since 1899, a well equipped and maintained medical library, adequately housed and supported, with a trained medical librarian in charge and containing 25,000 books and bound journals. The funds to support this library are derived from interest on a fund accumulated from the sale and manufacture of surgical ligatures, which enterprise was started by Dr. Edward Boeckmann over 40 years ago, and also from profits from the now defunct Saint Paul Medical Journal.

The medical practitioners of Saint Paul are proud of their past history and optimistic that their professional standing for the future is assured.

ANNALS OF INTERNAL MEDICINE

VOLUME 16

FEBRUARY, 1942

NUMBER 2

METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT. II. HEPATIC DYSFUNCTION*

By JULES C ABELS,† M D, PAUL E REKERS,‡ M D, GEORGE E BINKLEY,
M D, GEORGE T PACK, M D, and C P RHOADS, M D, F A C P,
New York, N Y

In a previous communication¹ it was demonstrated that about 85 per cent of patients with cancer of the gastrointestinal tract had abnormally low plasma levels of vitamin A. In the majority of these patients the levels were considered to be due to an inability of the livers of the patients to store the vitamin or to distribute it properly. It thus became desirable to study in greater detail the hepatic function of patients having cancer of the gastrointestinal tract, to correlate, if possible, the existence of hepatic dysfunction with the presence of the cancer, and finally, to note what relation the hepatic function might bear to the ability of patients to withstand operative procedures and to their postoperative course.

It was believed that an estimation of liver function in each patient could be obtained from the results of tests which measure the ability of the liver to synthesize, store, conjugate and excrete metabolites. Such studies were made of four groups of individuals: (a) normal adults, (b) patients with atrophic gastritis and leukoplakia of the oral mucosa, (c) patients with cancer of the gastrointestinal tract, and (d) individuals whose neoplasm had been successfully removed by surgery.

The existence of hepatic dysfunction in patients with cancer of the gastrointestinal tract is especially important because they are frequently subjected to prolonged anesthesia and to extensive surgical procedures which, by themselves, are injurious to normal livers^{2,3}. Further injury to an already damaged organ may give rise to serious problems in postoperative care.

* Received for publication October 27, 1941
From the Memorial Hospital, New York City

† Finney-Howell Fellow

‡ National Cancer Research Institute Fellow

CLINICAL MATERIAL

Twenty-five normal individuals were studied as controls to establish the normal incidence of hepatic dysfunction as measured by the tests employed in this investigation. The subjects were adults of both sexes, from 20 to 65 years of age, and all apparently in good health.

The clinical material studied consisted of four groups of patients. The first group included 62 patients with cancer of the alimentary tract. Five of these had cancer of the esophagus, 39 cancer of the stomach, and 18 cancer of the large intestine. The presence of a malignant epithelial neoplasm was established by one or more of the usual methods—namely, roentgenography, biopsy, endoscopy, or laparotomy. Forty-seven of the patients provided an opportunity for gross examination of the liver, either at operation or autopsy. In 15 instances metastatic nodules in the liver were found, but in none were they sufficiently extensive to suggest the possibility of anatomical impairment of hepatic function. Twelve of the patients with gastric cancer were employed only for a study of the cause of the hypoproteinemia associated with this disorder.

The patients with cancer of the esophagus and stomach received preoperatively liberal, well-balanced, hospital diets. However, three of the five patients with esophageal neoplasm were fed through gastrostomy tubes but these also were considered to receive adequate nutrition. Most of the individuals with cancer of the large bowel received preoperatively diets low in meat and rich in carbohydrate. Considerable vitamin supplements were not administered preoperatively to any of the patients.

Deep roentgen therapy was administered preoperatively to the pelvic region of 15 of the 18 patients with cancer of the large bowel.

The second group comprised 19 individuals whose gastrointestinal neoplasm had been surgically removed. In 12, the lesion originally was of the stomach, and in 7, of the large bowel. At the time of laparotomy a hepatic metastasis* was believed to be present in only one of 19, and that patient is now alive five years after operation. The studies were made from three months to 10 years after operation, and at that time no evidence of neoplastic disease was found.

The third group consisted of eight patients with atrophic gastritis. In all, the presence of the lesion was proved by gastroscopic examination, and all had symptoms referable to their disease.

The fourth group of patients represented 21 routine admissions to the Head and Neck Service of the hospital. All had leukoplakia of the oral mucosa and none had either cancer or syphilis.

No patient in any of the groups studied had any evidence of primary disease of the liver such as cirrhosis or hepatoma.

* This metastatic nodule was not biopsied.

METHODS

Liver function studies were not made on any patient until an adequate diet had been taken for at least two days. All the venepunctures were done in the morning when the patients were fasting. The observations on the patients with cancer of the gastrointestinal tract always were made preoperatively, and in many cases postoperatively also.

The procedures employed were as follows:

1 *Plasma Prothrombin* The so-called "bedside" technic of Warner, Brinkhouse, and Smith⁴ was employed. The values obtained have been found here and elsewhere to check very closely with the actual prothrombin levels as determined by the two-stage titration procedure.

2 *Serum Bilirubin* The measurement of serum bilirubin was made by the method of Soffer and Paulson.⁶ The extraction of bilirubin with acetone may not be quantitative, and this source of error would result in low values.

3 *Serum Proteins* The falling drop technic of Weech⁷ was employed, and the serum albumin and globulin by the technic described by Robinson et al.⁸

4 *Vitamin A* The method described in the previous communication¹ was used.

5 *Urinary Excretion of Glucuronates* These compounds were measured by the technic of Maugham et al.⁹

6 *Mean Corpuscular Volume of Erythrocytes* This was determined in whole citrated-oxalated blood as described by Wintrobe.¹⁰

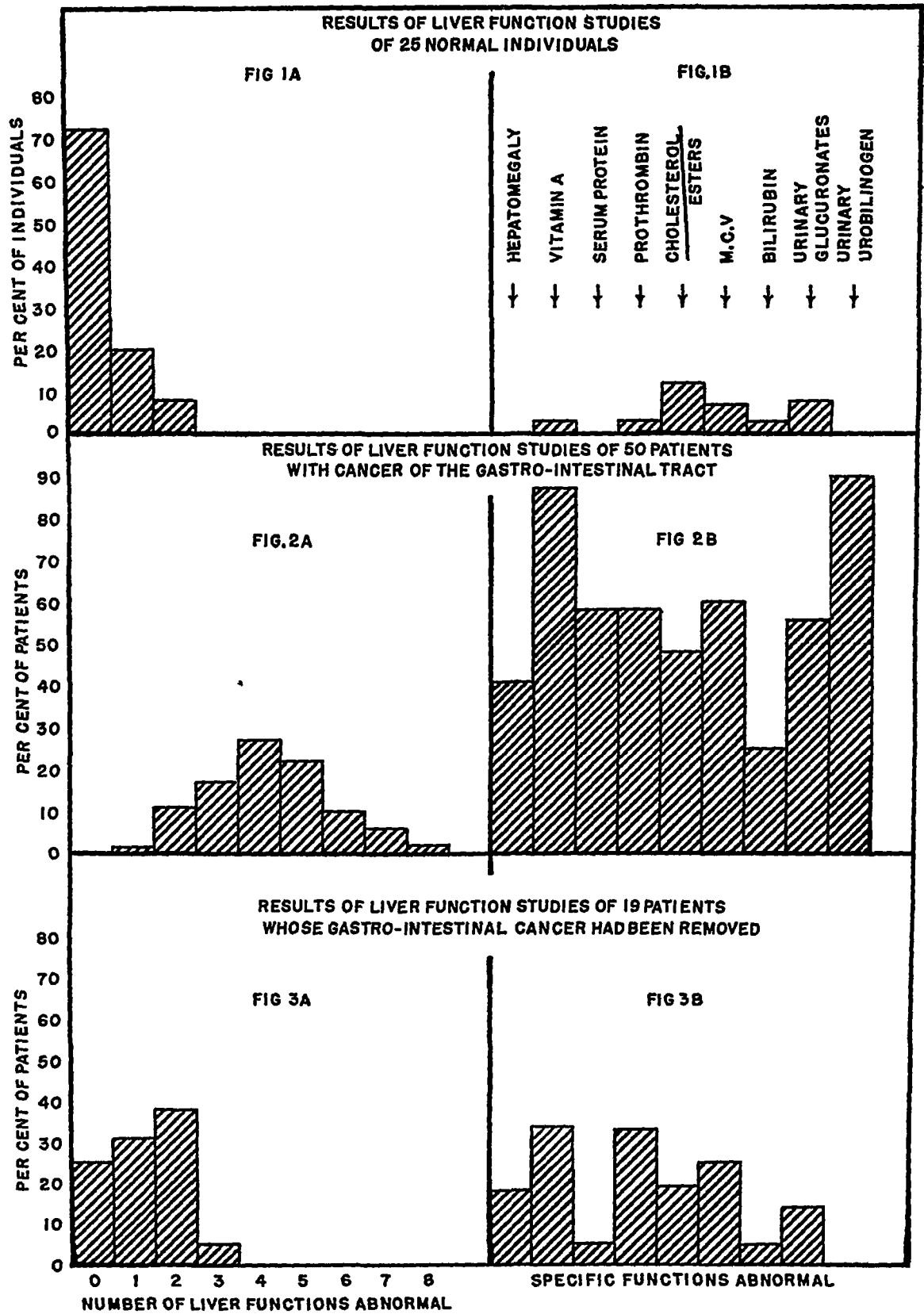
7 *Urinary and Fecal Excretion of Urobilinogen* The method of Watson¹¹ was used.

8 *Serum Cholesterol and Cholesterol Esters* These were measured in the serum by the method of Schoenheimer and Sperry.¹²

Hepatic abnormality was considered to be present when (1) the plasma prothrombin level was less than 85 per cent of the normal, (2) the serum bilirubin was above 1.0 mg per cent, (3) the total serum protein content was less than 6.6 grams per cent, and the albumin was less than 4.0 grams per cent associated with a globulin of more than 2.0 grams per cent, (4) the plasma level of vitamin A was less than 132 U.S.P. units in males and 103 U.S.P. units in females, (5) the urinary excretion of glucuronates was less than 300 mg per day, (6) the mean corpuscular volume of erythrocytes was greater than $94 \mu^3$, (7) the free cholesterol was more than 33 per cent of the total, (8) the urinary excretion of urobilinogen was more than 2.0 mg per day when the fecal output of the pigment was normal, and (9) hepatomegaly was demonstrable.

RESULTS

The studies described in this communication may be grouped under two headings. (A) The results of liver function studies in normal individuals and



in patients with cancer of the gastrointestinal tract, and (B) Evidence to explain the abnormal functions discovered in those patients

A The Results of Liver Function Studies in Normal Adults and in Patients with Cancer of the Gastrointestinal Tract

1 Normal Adults Twenty-five individuals were studied and the results are presented in figure 1, table 1. None had hepatomegaly or decreased

TABLE I
Results of Liver Function Studies on Normal Individuals

Individual	Sex	Age	Diet	Hepatomegaly	Plasma Vitamin A USP units per cent	Plasma Carotene, mg per cent	Plasma Prothrombin, per cent	Serum Protein gm per cent	Free Cholesterol/Cholesterol Esters mg per cent	Mean Corpuscular Volume u ³	Serum Bilirubin, mg per cent	Urine Glucuronate Excretion mg per day
J. A.	M	28	A*	No	150	0.22	100	7.3	70.2/140.1	91	50	816
D. T.	F	22	A	No	152	0.27	100	7.2	49.5/125.7	92	45	340
A. B.	F	23	A	No	170	0.195	100	7.7	48.9/101.1	84	60	423
A. R.	F	21	A	No	143	0.17	100	7.4	48.3/103.9	88	90	342
M. H.	F	26	A	No	92	0.40	100	6.8	63.9/149.9	92	50	464
N. N.	F	22	A	No	112	0.12	100	7.4	56/124.5	89	50	
L. W.	M	28	A	No	162	0.255	100	7.0	63.6/115.2	92	75	386
H. F.	F	41	A	No	185	0.25	100	6.6	58.1/153.4	94	50	1095
A. G.	F	30	A	No	115	0.30	100	7.8	44.2/104.6	77	58	446
M. P.	F	37	A	No	190	0.145	100	7.2	42.4/116.9	93	45	675
V. W.	F	24	A	No	104	0.10	100	7.0	46.8/123.5	96	75	362
N. T.	M	50	A	No	140	0.08	100	7.8	74/188	90	75	565
N. Y.	M	27	A	No	178	0.13	100	7.2	62.2/129.4	90	45	649
M. D.	M	29	A	No	163	0.19	100	7.1	53.2/129.8	94	45	414
K. S.	F	35	A	No	152	0.16	100	6.8	61/130	76	90	326
P. R.	M	32	A	No	200	0.32	100	7.0	49/120.9	83	50	362
W. D.	M	60	A	No	220	0.23	100	7.2	72.7/178.4	94	65	280
S. E.	F	24	A	No	150	0.38	100	7.0	60.6/120.9	93	170	383
G. R.	F	65	A	No	250	0.60	100	6.9	125.3/224.6	92	60	289
A. S.	F	25	A	No	150	0.52	94	6.8	63.5/174.9	93	65	356
B. L.	F	68	A	No	140	0.11	67	6.9	44.8/113.8	77	65	770
J. S.	M	61	A	No	225	0.10	100	7.3	70.2/208.8	90	60	308
C. B.	F	50	A	No	268	0.215	100	7.2	62.9/163.1	98	65	
A. G.	F	28	A	No	105	0.32	97	7.0	70/148	90	90	340
E. W.	F	50	A	No	105	0.35	90	7.2	146/349	75	65	348

* A = Adequate

concentrations of serum protein. Abnormal values of serum bilirubin, plasma prothrombin and plasma vitamin A were found once each (4 per cent) in the entire group. Two individuals (8 per cent) had macrocytosis and low urinary excretions of glucuronate. Three (12 per cent) had abnormally high levels of free cholesterol in the serum. However, only two of the 25 individuals had as many as two hepatic abnormalities.

2 Patients with Gastrointestinal Cancer The results of studies of patients with gastrointestinal cancer were in sharp contrast to those obtained in normal individuals. The findings indicated that all of the group of 50 patients examined had one or more abnormal finding (figure 2, table 2).

TABLE II

Results of Liver Function Studies in Patients Bearing Cancer of the Alimentary Tract

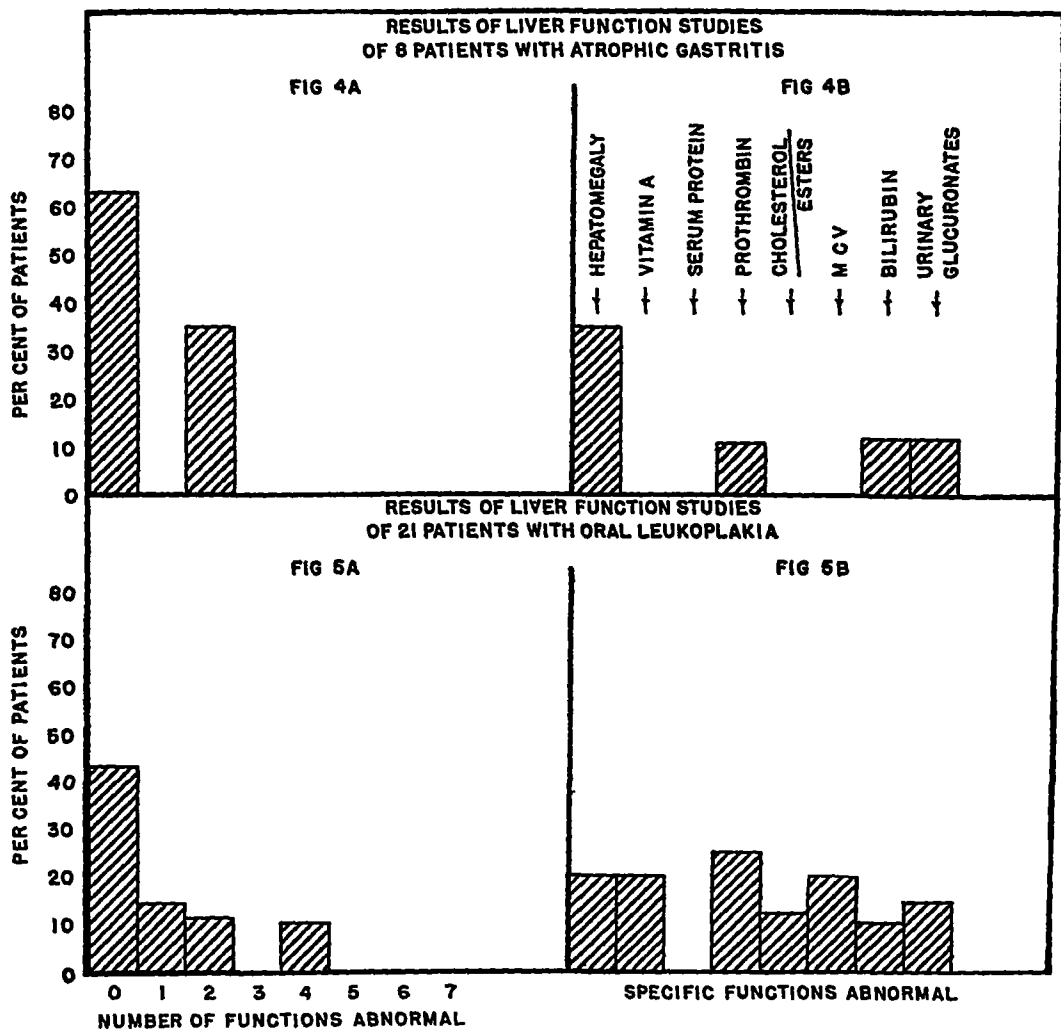
Patient	Sex	Age	Diet *	Site of Cancer	Operation	Liver Metastases	Wound Disruption	Transfusion Reaction	Achlorhydria	Hepatomegaly	Plasma Vitamin A, USP units per cent	Plasma Carotene, mg per cent	Plasma Prothrombin per cent	Serum Protein, gm per cent	Free Cholesterol/Cholesterol Esters, mg per cent	Mean Corpuscular Volume, μ^3	Serum Bilirubin, mg per cent	Urine Glucuronate Excretion, mg per day	Urinary Urobilinogen, mg per day
J A	M	35	D	Esoph	Yes	Yes			No	Yes	92	0 06	74	5 7	52/112	92	0 38		
B B	M	54	A	Colon	Yes	No	Yes		No	No	87	0 11	91	5 6		102	1 1		
K B	F	51	D	Stom	No	?			No	No	69	0 145	81	7 3	89/220	98	1 0	223	0 25
G B	M	40	A	Esoph	Yes	No			No	No	48	0 07	100	6 8	55/45	84	0 85	326	
D B	F	65	D	Stom	Yes	No			Yes	No	75	0 05	100	6 5	61/146	91	0 25	163	
E B	M	63	A	Stom	Yes	No			Yes	No	83	0 17	100	6 3		85	0 80	194	
F C	M	42	A	Stom	Yes	No				No	39	0 10	94	4 8	41/58	80	0 60	450	3 4
B C	M	55	A	Colon	Yes	No		Yes		No	65	0 085	84	5 9	56/91	80	0 7		
D C	M	64	A	Stom	Yes	No			Yes	Yes	107	0 09		5 7	52/89	85	0 33	277	
P L	M	51	A	Stom	Yes	No			No	No	139	0 075	80	7 6	66/174	82	0 60	224	
I D	M	54	A	Stom	Yes	No			Yes	Yes	179	0 045	100	6 9	100/140	100	0 50	208	
F F	M	62	A	Stom	Yes	No	Yes	Yes	Yes	Yes	67	0 065	75	6 4	49/114	80	0 45	173	
T F	M	67	A	Stom	Yes	No			Yes	Yes	120	0 12	83	6 2	46/103	100	0 60	98	
D G	M	72	A	Rect	No	?				No	138	0 115	100	6 4					
L G	M	55	A	Colon	Yes	No				No	98	0 16	75	7 2	61/135	78	0 50	117	
P G	M	53	D	Stom	Yes	No			Yes	No	138	0 095	97	6 0	29/62	100	1 15	532	
J K	M	52	D	Stom	Yes	No			Yes	No	125	0 13	88	7 3		92	0 4	447	4 8
K K	M	47	A	Colon	Yes	No				No	108	0 21	100	5 8	51/140	95	1 0	187	
M K	F	50	A	Stom	Yes	No				No	76	0 055	75	5 6	47/100	114	0 45	145	
G B	M	72	A	Stom	Yes	No			Yes	No	74	0 075	68	6 7	77/140	111	0 40	214	
I C	F	60	A	Colon	Yes	No	Yes	Yes		Yes	81	0 225	66	6 0	87/190	110	0 60	181	5 6
F C	F	38	A	Colon	Yes	No	Yes	Yes		Yes	54	0 075	100	4 8	78/128	105	0 50	376	12 5
D H	M	30	A	Stom	Yes	Yes		Yes		Yes	38	0 06	35	5 5	106/76	100	7 5	377	4 5
L L	M	57	A	Colon	No	No				No	112	0 07	62	7 3	72/79	101			
N L	M	72	A	Stom	Yes	No			Yes	Yes	31	0 11	90	4 9	58/147	110	4 5		
M M	F	44	A	Colon	Yes	Yes				Yes	72	0 055	84	6 8	75/140	105	0 68	170	
M M	F	63	D	Stom	No	?			Yes	No	147	0 27	100	6 5		100	1 0	156	
V N	F	68	A	Colon	No	Yes				Yes	98	0 15	78	6 3	177/348	102	0 88	167	5 75
A O	M	66	D	Stom	Yes	Yes			No	No	48	0 06	44	5 3	50/100	90	5 5	570	
P P	F	64	D	Colon	No	Yes				Yes	44	0 41	100	6 0	104/168	100	1 3	600	
F P	M	48	A	Stom	Yes	Yes			Yes	No	93	0 18	100	7 2	50/96	93	0 9	144	
L P	M	57	A	Stom	Yes	No				Yes	75	0 075	67	6 5		106	0 45	142	
J S	M	50	A	Stom	Yes	Yes			No	Yes	64	0 055	80	7 8	84/145	98	0 63	585	
O S	M	50	A	Sigm	Yes	No				Yes	110	0 05	75	7 8		130	0 38		
F T	M	43	A	Colon	Yes	Yes				No	112	0 12	75	6 4	53/111	104	0 4		
S T	F	45	A	Colon	No	?				No	70	0 17	92	6 0	31/62	80	0 45	17	
F W	M	37	A	Stom	Yes	No			Yes	No	73	0 175	67	7 1	48/102	80	0 70	435	30
L W	M	67	A	Stom	Yes	Yes				No	68	0 165	70	7 1		120	0 85	375	
L W	M	55	A	Colon	Yes	No			Yes	No	32	0 12	76	6 2	54/96	80	0 45	450	
R B	M	66	A	Stom	Yes	No				Yes	95	0 27	95	5 8	43/94	91	0 45	478	
R B	M	56	D	Stom	Yes	No			Yes	No	48	0 07	100	6 8	48/52	110	0 75	357	
W V	M	40	D	Esoph	Yes	No				No	93	0 07	85	6 6	60/80	103	0 6	248	
J E	F	48	A	Stom	Yes	No			Yes	Yes	60	0 21	56	7 1	51/78	100	0 63	378	
D R	M	69	A	Colon	Yes	No				No	30	0 13	76	6 8	60/78	84	0 60	54	
D Q	M	52	A	Stom	Yes	No			Yes	Yes	37	0 50	66	5 7		100	0 70		
R J	F	45	D	Esoph	Yes	No				No	65	0 085	98	7 2	52/124	112	1 45	364	
K P	M	58	A	Rect	Yes	No	Yes	Yes		Yes	122	0 105	69	5 7	59 5/95	110	2 20	496	
D B	M	62	A	Recto-sigm	Yes	No		Yes		No	125	0 095	98	7 7	61/252	90			
																	1 15		
D W	M	50	A	Stom	Yes	Yes			No	Yes	98	0 245	100	7 1	55/123	103	0 90	90	3 6
F W	M	27	D	Esoph	Yes	No			No	Yes	68	0 195	53	6 0	76/165	80	0 63	169	

* A = Adequate
D = Deficient

One patient (2 per cent) had but one abnormality, four (12 per cent) had two, nine (18 per cent) had three, 14 (28 per cent) had four, 11 (22 per cent) had five, five (10 per cent) had six, and four (8 per cent) had seven or more

Of the 50 patients, 21 (42 per cent) had hepatomegaly, 29 (58 per cent) had reduced levels of serum protein, and 45 (90 per cent) had low plasma levels of vitamin A. The concentration of prothrombin was reduced in the

plasma of 28 of the 48 patients examined (58 per cent) and the serum bilirubin elevated in 12 of the 47 (24 per cent) instances in which it was measured. Twenty-nine of 49 patients (60 per cent) had abnormally high MCV values and 20 of the 43 (45 per cent) had ratios of free to esterified



cholesterol in the serum greater than 1.2. The daily urinary excretion of glucuronates was reduced significantly in 23 of 41 (55 per cent) and that of urobilinogen increased in eight of nine (89 per cent) studied.

B Experiments to Determine the Cause of the Hepatic Insufficiency in Patients with Gastrointestinal Cancer

The most obvious explanations of the results of the tests of liver functions in the 50 patients with gastrointestinal cancer are (1) the replacement of their normal liver tissues by metastases from the gastrointestinal neoplasm, (2) malnutrition of the patient and consequently of the liver cells,

(3) the coexistence of the extrahepatic cancer, and (4) a combination of these factors

1 Hepatic Metastases It does not seem probable that the findings could have been due to metastatic disease of the liver. Exploratory laparotomy was performed in 41 of the 50 patients, and in only 13 of the 41 patients were any metastases to the liver found. The extent of the involvement in 11 of the 13 instances was considered to be minimal. In only two was there enough cancer tissue in the liver apparently to interfere with the function of that organ by compression of either the vascular or biliary circulation.

2 Malnutrition of the Patients and Consequently of the Liver Cells Since gastrointestinal disease was present, the possibility of simple malnutrition was considered. The fact has been shown repeatedly that a long continued inadequate diet will deplete the hepatic stores of labile protein,^{13, 14} glycogen,¹⁵ vitamins¹⁶ and antianemia principles¹⁷. These depleted livers are readily susceptible to further damage by toxic agents,^{2, 18, 19} and may become inefficient in the performance of other functions such as the excretion of bilirubin and fabrication of prothrombin.

The dietary histories of the 50 patients with gastrointestinal cancer revealed that only 12 had been on diets deficient in calories, proteins, or vitamins. The dietary intake of the other 38 was considered to be adequate by accepted standards. Nevertheless, the occurrence of hepatic dysfunction as manifested by the existence of hypoproteinemia, low plasma levels of vitamin A and prothrombin, and macrocytosis was as common among the 38 patients who had been on adequate diets as among the 12 whose diets were considered grossly deficient.

Of the 12 patients on inadequate diets, 87 per cent had low plasma levels of vitamin A, 58 per cent had hypoproteinemia and macrocytosis, and 42 per cent had hypoprothrombinemia. Likewise, of the 38 patients on apparently adequate diets, 87 per cent had low plasma levels of vitamin A, 58 per cent had hypoproteinemia, 64 per cent had hypoprothrombinemia, and 60 per cent had macrocytosis.

In order to determine whether the low plasma levels of vitamin A and prothrombin of the patients with gastrointestinal cancer were due to an inadequate ingestion of vitamins A and K, or to some other reason, several patients were given large amounts of those vitamins and measurements of vitamin A and prothrombin were subsequently made in their plasma.

(a) *Vitamin A* Eight unselected patients with cancer of the gastrointestinal tract and low plasma levels of vitamin A were given from 50,000 to 150,000 U.S.P. units of vitamin A for from 7 to 20 days. These amounts of vitamin A are sufficient to raise the low levels of the vitamin in the plasma of individuals on low vitamin A diets^{1, 20, 21}. The vitamin was administered orally to one patient, parenterally to six, and both orally and parenterally to one. Only one of these patients was known to have been on a deficient diet. After the administration of the vitamin, the plasma level

rose in two of eight instances. In the other six the plasma levels of vitamin A were from 5 to 33 per cent less than they had been before the administration of the vitamin supplements (table 3)

TABLE III
Results of the Administration of Vitamin A to Patients with Cancer
of the Gastrointestinal Tract

Patient	U S P Units of Vitamin A Administered	Mode of Admini- stration	Plasma Vitamin A	
			Pre-Therapy	Post-Therapy
J D	900,000	1 m	96	92
F F	1,050,000	1 m	128	48
E B	630,000	p o	116	164
M H	500,000	p o	108	72
	400,000	1 m		
F W	800,000	1 m	88	76
D W	2,000,000	1 m	92	68
F P	750,000	1 m	88	64
M S	500,000	1 m	100	176

(b) *Vitamin K* In a similar manner six unselected patients with gastrointestinal cancer and with low plasma levels of prothrombin were given daily 2 mg of synthetic vitamin K * parenterally for from two to three days. It has been shown that 10 mg of vitamin K will cause a substantial rise in the low plasma prothrombin levels when a dietary deficiency or malabsorption of the substance is present²². However, the administration of from four to six times the therapeutic dose to the six patients studied failed to induce any significant change in their concentrations of plasma prothrombin (table 4). After the vitamin K therapy, the prothrombin levels of the six patients studied rose in three only from 7 to 18 per cent, fell in one, and was not altered in two patients.

TABLE IV
Results of Parenteral Administration of Synthetic Vitamin K to Patients
with Cancer of the Gastrointestinal Tract

Patient	Pre-Vitamin K per cent	Prothrombin Level
		Post-Vitamin K per cent
W C	55	65
J B	72	77
W B	59	69
D R	58	59
L D	81	54
S H	49	49

(c) *Serum protein* Hypoproteinemia was found in 29 of the 50 patients studied, and in only seven instances could histories of diets deficient in protein be elicited. It is possible, nevertheless, that the information obtained concerning the protein intake was inaccurate, and that the frequent

* 2 methyl 1, 4 naphthoquinone

occurrence of hypoproteinemia must be regarded not as a result, but as a cause of hepatic insufficiency

The fact has been demonstrated repeatedly²³ that the albumins are manufactured principally by the liver cells. Hence, low serum levels of albumin in the presence of normal concentrations of serum globulin would be more likely to reflect an inability of the liver to synthesize albumin than to indicate an inadequate protein intake. For that reason it was deemed important to determine whether or not the hypoproteinemia found in patients with cancer of the gastrointestinal tract was due chiefly to hypoalbuminemia.

Determinations of serum albumin and globulin were made in 12 patients, only three of whom had been on grossly inadequate diets. Of these 12 patients, 11 had concentrations of serum protein under 6.5 per cent, and of the 11, 10 had concentrations of serum albumin under the accepted low level of 4.0 grams per cent. In only two of the 10 patients were these levels of hypoalbuminemia associated with levels of serum globulin of less than 2.0 grams per cent (table 5), and those two patients had been on deficient

TABLE V

The Concentrations of Total Protein, Albumin and of Globulin in the Serum of Patients with Cancer of the Gastrointestinal Tract

Patient	Diet	Total Serum Protein, gm per 100 ml	Serum Albumin gm per 100 ml	Serum Globulin, gm per 100 ml
F B	Adequate	6.60	4.26	2.34
D S	Adequate	6.25	3.40	2.85
A N	Adequate	6.19	3.72	2.47
S G	Adequate	5.90	2.85	3.15
F K	Adequate	5.90	3.32	2.58
J M	Adequate	6.45	3.90	2.55
F R	Adequate	5.36	3.26	2.10
H G	Adequate	5.98	3.96	2.02
D M	Adequate	5.45	3.04	2.41
J R	Inadequate	4.83	3.36	1.47
E W	Inadequate	5.70	4.24	1.36
K P	Inadequate	4.64	2.92	1.72

diets. Thus, it would appear that the hypoproteinemia found in 11 patients could be explained in 10 instances by a decreased concentration of the albumin fraction, and that in eight of the 10 the hypoalbuminemia was due to an impaired fabrication and not to a decreased dietary intake of protein.

In short, from such experiments as could be performed, it appeared that the frequent occurrence of low plasma levels of vitamin A and prothrombin at least are not due to inadequate diets, but rather to a specific disorder which prevented the normal distribution by the liver of vitamin A or the utilization of vitamin K. Likewise, the occurrence of hypoproteinemia in many of the patients is due probably to an impaired ability of the liver to synthesize albumin and not to an inadequate dietary intake of protein.

Although the evidence at hand indicated that inadequate diets probably could not explain the high incidence of hepatic dysfunction in patients with

PATIENTS WITH CANCER OF GASTROINTESTINAL TRACT

gastrointestinal cancer, one could not be satisfied that the normal values used for comparison were valid controls, since the normal subjects differed considerably in age and in economic and dietary background from the patients. Hence, it was important to control further these factors.

Accordingly, measurements were made of the hepatic function of two other groups of patients—one with atrophic gastritis, and the other with leukoplakia of the oral mucosa. The patients of these groups were of an age and dietary and economic background similar to those with gastrointestinal cancer.

TABLE VI
Results of Liver Function Studies in Patients with Atrophic Gastritis

Patient	Sex	Age	Diet	Hepatomegaly	Plasma Vitamin A USP units per cent	Plasma Carotene mg per cent	Plasma Prothrombin, per cent	Serum Protein gm per cent	Free Cholesterol/Cholesterol Esters mg per cent	Mean Corpuscular Volume, μ^3	Serum Bilirubin, mg per cent	Urine Glucuronate Excretion mg per day
L O	F	42	D	Yes	169	0 15	90	7 3	79/138	80	0 58	455
W N	M	57	\	No	216	0 08	100	7 6	70/151	78	0 65	495
D S	M	45	\	No	130	0 09	100	7 8	54/108	74	0 70	522
A D	F	40	A	Yes	132	0 08	100	6 8	64/147	90	0 94	119
G K	M	62	D	No	121	0 14	100	6 6	85/175	85	0 63	400
S U	F	50	A	Yes	215	0 20	100	6 9	39/94	83	1 13	686
A S	F	43	A	No	138	0 21	96	7 8	64/135	81	0 88	560
I R	M	62	A					7 3	88/209	86	0 63	

In eight patients with atrophic gastritis (figure 4, table 6), a lesion sometimes held to be precancerous,²⁴ little evidence could be found for the existence of hepatic disease. Two of the eight had been on grossly inadequate diets but none had low plasma levels of vitamin A, hypoproteinemia, macrocytosis, or hypoprothrombinemia. Only one patient had an increased level of serum bilirubin, a second had a decreased urinary output of glucuronates serum cholesterol, and a third had an increased ratio of free to esterified cholesterol.

However, it is interesting to note that three of the eight had hepatomegaly. Five of the eight were entirely free of evidence of liver disease. Of 21 patients with oral leukoplakia (figure 5, table 7), four of 20 (20 per cent) had hepatomegaly, two of 19 (10 per cent) had hyperbilirubinemia, none of 19 had hypoproteinemia, four of 21 (19 per cent) had low levels of plasma vitamin A, one of four (25 per cent) had an abnormally decreased plasma prothrombin, one of 16 (6 per cent) had an increased ratio of serum cholesterol to cholesterol esters, four of 17 (24 per cent) had a decreased urinary output of glucuronates.

Of the abnormalities considered to indicate hepatic dysfunction, none were found in nine patients with oral leukoplakia, one in seven, two in three, and four in one. Seven of the 21, or 33 per cent, had been on grossly deficient diets.

TABLE VII
Results of Liver Function Studies on Patients with Oral Leukoplakia

Patient	Sex	Age	Diet *	Hepato-megaly	Plasma Vitamin A USP units per cent	Plasma Carotene, mg per cent	Plasma Prothrombin, per cent	Serum Protein, gm per cent	Free Cholesterol/Cholesterol Esters, mg per cent	Mean Corpuscular Volume u ³	Serum Bilirubin, mg per cent	Urinary Glucuronate Excretion mg per day	Urobilinogen Urine, mg per day
D B	F	55	A	No	192	0 137		7 1		90	45	300	34
L D	M	7	D	Yes	116	0 16		7 1 7 5	72/144	85	80	340	32
B B	F	62	D		160	0 04			70/171	82	87	363	
A C	F	66	A	No	269	0 18		7 2	60/147	100	90	283	
T R	M	44	A	No			80	8 5	79/181	81	45	582	
J R	M	38	D	No	138	0 275		6 9	66/155	90		290	
E M.	M	46	A	No	85	0 57		7 8	43/107	80	25		
F N	M	56		Yes	51	0 22		6 9	68/164	84	90	436	
W N	M	69	A	No	169	0 15	100	7 6	70/151	75	65	495	
J S	M	50	A	No	140	0 21			70/146	77		514	
J B	F	70	A	No	170	0 19		7 8		83	90	379	
A J	F	61	D	No				8 2	82/181	82	3 5		
E S	M	66	D	No	215	0 11	93	6 7	60/151	97	75	324	
A P	M	41	D	No	185	0 226		6 6	51/199	86	45	438	
C K	M	63	A	Yes	140	0 11		7 7	76/104	73	1 08	100	
H K	M	54	A	No	188	0 18		7 0	51/128	73	58		
A B	M	45	A	No	193	0 11		7 1	50/123	87	90		
J F	M	51	A	No	163	0 22		7 4			75	458	
L F	M	80	A	No	110	0 11		7 0	60/150	95	63	475	
S J	M	54	A	No	331	0 225		7 3		95	70	537	
M. K	M	46	D	Yes	381	0 107	100	7 4	42/191	86	50	205	

* A = Adequate
D = Deficient

A comparison of the findings in the patients with leukoplakia and atrophic gastritis with the findings in patients with cancer of the gastrointestinal tract seems to provide sufficient proof that the factors of age, dietary and economic background of the latter group were not responsible for the high incidence of hepatic dysfunction

3 *The Coexistence of Extrahepatic Cancer* If the hepatic dysfunction of patients with gastrointestinal cancer is the result of the neoplastic process, then, when the tumors were completely removed, an improvement of hepatic function should be expected. Such improvement only would be possible, however, if too much organic disease had not occurred in the liver and if the process were reversible

Studies of liver functions were made in 19 patients whose gastrointestinal cancer had been removed successfully. These patients had survived for from three months to 10 years, and were apparently still free of disease. Twelve originally had had cancer of the stomach and seven cancer of the large bowel, of the 19 patients, three had been on grossly deficient diets for at least four months before the liver function studies were performed

The results obtained by the examination of the hepatic function of these patients (figure 3, table 8) clearly indicate that the incidence and severity of

PATIENTS WITH CANCER OF GASTROINTESTINAL TRACT

TABLE VIII

Results of Liver Function Studies on Patients Who Have Had a Cancer of the Alimentary Tract Removed

Patient	Sex	Age	Diet ¹	Hepatomegaly	Site of Cancer	Survival Period Post Op., months	Plasma Vitamin A, USP units per cent	Plasma Carotene mg per cent	Plasma Prothrombin, per cent	Serum Protein, gm per cent	Free Cholesterol/Cholesterol Esters, mg per cent	Mean Corpuscular Volume, μ^3	Serum Bilirubin, mg per cent	Urine Glucuronate Excretion mg per day
L B	F	56	A	No	Stom	60	82	0.28	90	6.7	119/281	89	0.90	359
N C	M	61	A	No	Stom	60	380	0.11	100	8.1	66/81	80	0.65	351
J A	F	55	D	No	Stom ²	12	132	0.10	100	6.9		95	0.65	312
A C	M	45	A	Yes	L B	2	160	0.15	77	6.7	39/134	91	0.75	
I A	F	49	A	No	L B	70	172	0.08	100	7.7	62/128	74	0.75	322
A A	M	47	A	Yes	Stom	6	272	0.06	86	7.3	43/87	96	0.50	680
W E	M	40	A	Yes	Duo	12	90	0.02	94	6.2	43/89	90	0.40	600
M P	F	63	A	No	Stom	2	122	0.13	56	7.7	49/105	90	0.65	544
E T	M	41	A	No	Stom	96	122	0.10	94	7.0	58/118	90	2.00	544
K Z	M	58	A	No	Stom	60	125	0.16	98	7.1	53/126	90	0.70	330
J S	M	50	A	No	L B	62	232	0.03	95	7.5	74/143	99	0.75	189
A S	F	68	A	No	Stom	60	62	0.11	90	7.9	68.5/201	93	0.75	220
M E	M	58	A	No	L B	16	352	0.18	63	7.1	80/217	95	0.75	
J S	F	72	A	No	L B	4	208	0.12	100	7.6	57.5/108	90	0.90	617
A E	F	65	A	No	Stom	40	88	0.09	88	7.7	70/197	89	0.75	775
M I	F	54	A	No	L B	31	132	0.12	92	8.1	71/207	85	0.50	330
G B	F	48	D	No	Stom	8	270	0.25	80	7.2				
H S	M	47	A	No	L B	53	210	0.07	74					
I C	F	48	A	No	Stom	15								
E L	F	48	A	No										
A J	M	56	A	No										

¹ A—Adequate diet
² Total gastrectomy
³ Reported to have metastases to liver at time of operation
⁴ Pancreatic insufficiency

D—Deficient diet No biopsy obtained

hepatic dysfunction in this group are much less than those found in the group of patients still bearing gastrointestinal cancer. Of the 19 patients, hepatomegaly was present in three (16 per cent), hyperbilirubinemia and hypoproteinemia each in one (5 per cent), hypoprothrombinemia in six (33 per cent), and low plasma levels of vitamin A in seven (34 per cent). An increased ratio of cholesterol to cholesterol esters was noted in three of 16 (19 per cent) and macrocytosis in four of 17 instances (23 per cent). Reduced excretions of urinary glucuronates were found in only two of 14 patients (14 per cent).

No evidence of hepatic disease was found in five of the 19 patients. Only one of the nine criteria for hepatic dysfunction was found to exist in six patients, two in seven, and three in one (figure 3).

Thus, a comparison of the results of these studies with those of comparable studies made in patients still bearing active cancer show striking differences (table 9). Among the patients bearing active cancer of the gastrointestinal tract, the incidence of hepatomegaly is 2.6 times as great as that in the patients with such tumors removed. Likewise, the incidence of low plasma levels of vitamin A is 2.7 times as great, of hypoprothrombinemia, 1.8 times,

TABLE IX

Comparison of the Results of Liver Function Studies Obtained in Normal Individuals and in the Groups of Patients Studied

	Normals	Leukoplakia of the Oral Mucous Membranes	Atrophic Gastritis	Cancer of the Gastro- intestinal Tract	Cancer of the Gastro- intestinal Tract Removed
Number of Patients	25	21	8	50	19
Hepatomegaly	0%	20%	37 5%	42%	16%
Elevated Serum Bilirubin	4%	10%	12 5%	24%	5%
Decreased Serum Protein	0%	0%	0%	58%	5%
Decreased Plasma Prothrombin	4%	25%	0%	58%	33%
Impaired Cholesterol Esterification	12%	6%	12 5%	45%	19%
Increased MCV of Erythrocytes	8%	20%	0%	60%	23%
Decreased Plasma Vitamin A	4%	19%	0%	90%	34%
Decreased Urinary Excretion of Glucuronates	8%	24%	12 5%	55%	14%

of macrocytosis, 2 5 times, of hyperbilirubinemia 5 0 times, of increased ratios of free to esterified cholesterol, 2 6 times, and finally, of decreased urinary daily output of glucuronates, 6 2 times that found in patients whose tumors had been removed

In summary, therefore, it appears that no significant hepatic dysfunction exists in patients with atrophic gastritis, that it is pronounced in patients bearing a cancer of the gastrointestinal tract, and it is considerably less prominent among patients whose cancer has been removed successfully

DISCUSSION

Inasmuch as the liver performs multiple functions, it is reasonable to believe that no single test can measure adequately the efficiency of the whole organ. By the measurement qualitatively, and when possible quantitatively, of various intermediary or end products of liver metabolism and then by the consideration of the results as a whole, it is felt that abnormal function can be detected.

Liver function tests at the best are crude. The exact amount of liver tissue that can be destroyed before an abnormal result of any test can be noted is unknown, but it is probably considerable. Experimentally, it has been shown that from one-half to two-thirds of the liver can be damaged and the organ will still regenerate and return to normal²⁵. Disease of the liver may progress to a far advanced stage before symptoms result or changes are produced which indicate hepatic dysfunction.

In this study measurements of liver function were selected arbitrarily. It is, therefore, necessary to consider the evidence which would indicate that the tests employed in this study are adequate measurements of hepatic function.

Prothrombin. There is considerable evidence to show that the liver is the site of prothrombin formation.²⁶ A fall of the prothrombin level con-

sistently parallels liver injury, and the level of that substance returns to normal as the liver regenerates.²⁷ Decreased plasma prothrombin levels follow operations,⁷ certain anesthetics,²⁸ trauma to the liver,²⁹ cirrhosis, obstructive jaundice,³⁰ and prolonged malnutrition with depleted nutritional stores.³¹

Serum Bilirubin It is well established that the increase of bilirubin in the plasma parallels the inability of the liver to excrete that pigment. In the absence of increased intravascular lysis, hyperbilirubinemia must signify hepatic impairment.³²

Total Protein, Albumin and Globulin The liver is of primary importance in the formation, storage and exchange of plasma protein.³³ Fibrinogen is produced only by the liver cells,³³ and the best available evidence indicates that the albumins, likewise, are formed by that organ.⁶

Abnormal levels of circulating serum or plasma protein are reached only when the protein stores, chiefly in the liver, are decreased. The normal individual, depleted of his protein stores, readily can synthesize albumin, globulin and fibrinogen from a proper mixture of amino acids,³³ but those proteins are deposited first in the liver and other organs, and do not appear in the plasma until the body stores are reestablished. In a damaged liver the synthesis of protein from amino acids may be altered³⁴ and the circulating concentrations of plasma protein continue to decrease with further hepatic damage. The disappearance of the hepatic stores of protein with damage to the organ now has been shown by experiments which employ Eck fistula dogs³⁵ as well as by clinical studies of patients with hepatic cirrhosis.²³

Vitamin A There is reason to believe that many patients with hepatic insufficiency have low levels of vitamin A in their plasma. Of 25 patients with unequivocal cirrhosis, 16 had plasma levels of vitamin A below that of the lowest normal.³⁶ This finding of low plasma levels of vitamin A in hepatic cirrhosis also has been noted by others.³⁷ Clinical improvement of the patients with cirrhosis usually is associated with an increased amount of vitamin A in the plasma.

Glucuronic Acid It has been demonstrated that several aromatic compounds normally are conjugated with glucuronic acid and excreted as glucuronates in the urine.³⁸ This conjugation has been considered by several investigators to be a form of detoxification. The liver is the chief site for this synthesis of glucuronates. The kidney is the only other organ known to produce glucuronates, but its capacity for that production is only from one-tenth to one-sixth that of the liver. Livers injured by phosphorus soon lose their capacity to make glucuronic acid.³⁹

Mean Corpuscular Volume Macrocytosis affects the majority of red blood cells in the anemia associated with cirrhosis of the liver. One-half of 37 patients with hepatic disease were found to have macrocytosis, whereas hypochromic anemia was noted only when the patients suffered simultaneously from chronic blood loss. In all likelihood, this macrocytic anemia is due to an inability of the liver to store the necessary hematopoietic prim-

ciple, for certain livers removed at autopsy from patients with hepatic cirrhosis or necrosis appear to have been ineffectual in the treatment of pernicious anemia ⁴⁰

Urinary Urobilinogen If the fecal excretion of urobilinogen is within normal limits, the urinary excretion of that substance is considered to be a valuable index of hepatic function. It has been demonstrated that, under normal conditions, most of the urobilinogen absorbed from the gastrointestinal tract into the blood stream is converted by the liver cells into bilirubin ^{41, 47}. The rate of that conversion, therefore, must be impaired when excessive amounts of urobilinogen appear in the urine.

Cholesterol and Cholesterol Esters The serum concentration of total cholesterol and the ratio of free to esterified cholesterol in the normal healthy individual is maintained within rather narrow limits. From the best evidence at hand, it appears that the esterification of this sterol is accomplished chiefly in the liver ⁴⁸. Therefore, changes in the ratio of free to esterified cholesterol are of great significance.

In conclusion, it would appear that the tests employed in this study when considered as a group provide an adequate index of hepatic function. It is recognized that this study is incomplete and the use of other measurements of hepatic function, such as the excretion of bilirubin or bromsulphthalein, and the conversion of galactose would have been desirable, but at the time of this study such methods were not available in this laboratory.

Even in the normal individual the administration of anesthetics ² and the manipulation of the liver ³ have been shown to induce hepatic insufficiency. Therefore, it could be expected that in patients who already have physiologically damaged livers such procedures would result in more marked, and less well-tolerated, hepatic dysfunction. It has been demonstrated that the normal liver will recover completely from the effects of the administration of inhalation anesthetics, but the damaged organ, further impaired by toxic agents, may not return even to its previously reduced functional capacity ^{2, 44, 15}. Since patients with cancer of the gastrointestinal tract frequently undergo of necessity prolonged anesthesia and handling of the liver, their associated hepatic disease thus would add to the risks entailed by those procedures. Most of the 50 patients herein reported received combinations of large amounts of barbiturates both by mouth and intravenously. These drugs, known to be detoxified by the liver, ¹⁸ must impose an added load on an already damaged organ.

The frequent occurrence of hypoproteinemia, whether due primarily to impaired hepatic fabrication or to inadequate dietary intake of protein, has a special significance in these patients because of its direct relationship to delayed wound healing ¹⁶. The process of wound healing is a phenomenon of growth, and the repair and tensile strength of wounds are direct functions of fibroblastic proliferation and collagen formation. Reduction in the labile protein stores alters the formation of collagen and impairs fibroblastic activity.

and the growth of the corium.¹⁷ These alterations thus could result in delayed wound healing and even lead to wound disruption. The edema naturally occurring at wound edges is intensified and of longer duration in the presence of hypoproteinemia.⁴⁶

The fact is to be emphasized that hypoproteinemia in patients with hepatic disease is not to be considered a transient phenomenon although originally it might have been due to dietary deficiency or to blood loss. Hypoproteinemia in these patients represents a decrease in labile protein stores, and, because of previous or consequent hepatic damage, the impaired fabrication of plasma proteins must aggravate the hypoproteinemia.

The high incidence of macrocytic anemia in the patients with gastrointestinal cancer, likewise, probably plays an important rôle in their postoperative course. Anemic patients are believed to be less resistant to infections, and it is a common clinical observation that patients with tumors of the alimentary tract frequently manifest infection in the tumor, peritoneal cavity, or wounds as a result of inevitable contamination at the time of operation.¹⁸ To aggravate this already serious situation,^{49, 50} hepatic insufficiency is usually refractory to therapy.

Finally, not only does hepatic damage impose an augmented hazard in the patients subjected to anesthetics and operative procedures, but also to the transfusion of blood. This subject is discussed in detail in a subsequent report. Of the 50 patients reported in this communication 42 received transfusions and of these 42, 10 manifested severe hemolytic reactions. It has been shown that the incidence of hepatic dysfunction is considerably less in patients who had had a neoplasm of the gastrointestinal tract removed. This observation would suggest that the presence of the cancer had resulted in hepatic insufficiency which to a large extent was reversible.

CONCLUSIONS

- 1 Patients with cancer of the gastrointestinal tract show a very high incidence of hepatic dysfunction
- 2 The incidence of hepatic dysfunction is considerably less in patients who have had cancer of the gastrointestinal tract removed surgically
- 3 The incidence of hepatic dysfunction is considerably less in patients with such lesions as atrophic gastritis and leukoplakia of the oral mucous membranes
- 4 The existence of hepatic dysfunction in patients with cancer of the gastrointestinal tract is especially important because of the augmented hazard it imposes on their operative and postoperative course. Delayed wound healing, refractory anemia, hemolytic reactions to transfusion, hypoproteinemia and hypoprothrombinemia may all be associated with and possibly are due to liver insufficiency

The authors gratefully acknowledge the assistance given by Standard Brands, Inc., the Jane Coffin Childs Fund and the Dazian Foundation

BIBLIOGRAPHY

- 1 ABELS, J C, GORHAM, A T, PACK, G T, and RHOADS, C P Metabolic studies in patients with cancer of the gastro-intestinal tract I Plasma vitamin A levels in patients with malignant neoplastic disease, particularly of the gastro-intestinal tract, *Jr Clin Invest*, 1941, xx, 749-764
- 2 MILLER, L L, and WHIPPLE, G H Chloroform liver injury increases as protein stores decrease studies in nitrogen metabolism in these dogs, *Am Jr Med Sci*, 1940, cxcix, 204-216
- 3 LORD, J W, ANDRUS, D W, and MOORE, R A Plasma prothrombin in dogs with normal livers, *Arch Surg*, 1940, xli, 585-595
- 4 ZIFFREN, S E, OWEN, C A, HOFFMAN, G R, and SMITH, H P A simple bedside test for control of vitamin K therapy, *Am Jr Clin Path*, 1940, x, 13-16
- 5 WARNER, E D Vitamin K, theoretical and practical considerations, *New Internat Clin*, 1940, ii, 93-103, J B Lippincott Co, Philadelphia
- 6 SOFFER, L J, and PAULSON, M Comparative advantages and further modification of the bilirubin excretion test for hepatic function, *Am Jr Med Sci*, 1936, cxcii, 535-540
- 7 WEECH, A A, REEVES, E B, and GOETTSCH, E The relationship between the specific gravity and protein content in plasma, serum, and transudate from dogs, *Jr Biol Chem*, 1936, cxiii, 167-174
- 8 ROBINSON, H W, PRICE, J W, and HOGDEN, C G The estimation of albumin and globulin in serum, *Jr Biol Chem*, 1937, cxx, 481-498
- 9 MAUGHAM, G B, EVELYN, K A, and BROWNE, J S L A method for the quantitative estimation of glucuronic acid and conjugated glucuronides, *Jr Biol Chem*, 1938, cxxvi, 567-572
- 10 MUSSEY, J H, and WINTROBE, M M Tice system of medicine, 1940, vi, 795, W F Prior Co, Hagerstown, Md
- 11 WATSON, C J Concerning urobilinogen I An improved method for the approximate quantitative estimation of urobilinogen in urine and feces, *Am Jr Clin Path*, 1936, vi, 458-475
- 12 SCHOENHEIMER, R, and SPERRY, W M Micromethod for the determination of free and combined cholesterol, *Jr Biol Chem*, 1934, cvi, 745-760
- 13 McNAUGHT, J B, SCOTT, V C, WOODS, F M, and WHIPPLE, G H Blood plasma protein regeneration controlled by diet effect of plant proteins compared with animal proteins, influence of fasting and infection, *Jr Exper Med*, 1936, lxiii, 277-301
- 14 HOLMAN, R H, MAHONEY, E B, and WHIPPLE, G H Blood plasma protein regeneration controlled by diet, *Jr Exper Med*, 1934, lix, 251-267
- 15 DAVIS, N C, and WHIPPLE, G H Influence of drugs and chemical agents on the liver necrosis of chloroform anesthesia, *Arch Int Med*, 1919, xxiii, 636-654
- 16 BESSEY, O A, and WOLBACH, S B The vitamins, Chapter II, p 29, 1939, Am Med Assoc, Chicago
- 17 SCHUMACKER, H B, JR, and WINTROBE, M M Morphologic changes in blood associated with experimentally produced hepatic damage, *Bull Johns Hopkins Hosp*, 1936, lviii, 343-377
- 18 SMITH, H P, ZIFFREN, S E, OWEN, C A, and HOFFMAN, G R Clinical and experimental studies on vitamin K, *Jr Am Med Assoc*, 1939, cxiii, 380-383
- 19 MOON, V H Experimental cirrhosis in relation to human cirrhosis, *Arch Path*, 1934, xviii, 381-424
- 20 STFININGFR, G, ROBERTS, L J, and BRENNER, S Vitamin A in the blood of normal adults the effect of depletion diet on the blood value and biophotometric readings, *Jr Am Med Assoc*, 1939, cxiii, 2381-2387
- 21 MURRILL, W A, HORTON, P B, LIEBLMAN, E, and NEWBURGH, L Vitamin A and carotene II The vitamin A and carotene metabolism in diabetics and normals, *Jr Clin Invest*, 1941, xx, 395-400

- 22 BRINKHOUS, K M, and WARNER, E D Effect of vitamin K on hypoprothrombinemia of experimental liver injury, *Proc Soc Exper Biol and Med*, 1940, xlv, 609-610
- 23 MADDEN, S C, and WHIPPLE, G H Plasma proteins their source, production and utilization, *Physiol Rev*, 1940, xx, 194-217
- 24 RHOADS, C P Gastric cancer as a sequel to gastritis, particularly the gastritis of pernicious anemia, *Jr Nat Cancer Inst* 1941, i, 511-522
- 25 DAVIS, N C, HALL, C C, and WHIPPLE, G H The rapid construction of liver cell protein on a strict carbohydrate diet contrasted with fasting The mechanism of protein sparing action of carbohydrate, *Arch Int Med*, 1919, xxiii, 689-710
- 26 WARNER, E D, BRINKHOUS, K M, and SMITH, H P Quantitative study on blood clotting prothrombin fluctuations under experimental conditions, *Am Jr Physiol*, 1936, cxiv, 667-675
- 27 LORD, J W, ANDRUS, D W, and MOORE, R A Metabolism of vitamin K and role of liver in production of prothrombin in animals, *Arch Surg*, 1940, xli, 585-595
- 28 CULLEN, S C, ZIFFREN, S E, GIBSON, R B, and SMITH, H P Anesthesia and liver injury, with special reference to plasma prothrombin levels, *Jr Am Med Assoc*, 1940, cxv, 991-994
- 29 LORD, J W Effect of trauma to liver on plasma prothrombin, experimental study, *Surgery*, 1939, vi, 896-898
- 30 SCANLON, G H, BRINKHOUS, K M, WARNER, E D, SMITH, H P, and FLYNN, J F Plasma prothrombin and bleeding tendency with special reference to jaundiced patients and vitamin K therapy, *Jr Am Med Assoc*, 1939, cxii, 1898-1901
- 31 KARK, R, and LOZNER, E L A study of four non-jaundiced patients with dietary deficiency, *Lancet*, 1939, ccxxxvii, 1162-1163
- 32 RICH, A R Extrahepatic formation of bile pigment, *Bull Johns Hopkins Hosp*, 1925, xxvi, 233-247
- 33 DRURY, D R, and MACMASTER, P D The liver as the source of fibrinogen, *Jr Exper Med*, 1929, i, 569-578
- 34 CATES, H B Relation of liver function to cirrhosis of liver and to alcoholism comparison of results of liver function tests with degree of organic change in cirrhosis of liver and with results of such tests in persons with alcoholism without cirrhosis of liver, *Arch Int Med*, 1941, lxxii, 383-398
- 35 KNUTTI, R E, ERICKSON, C C, MADDEN, S G, REKERS, P E, and WHIPPLE, G H Liver function and blood plasma protein formation, normal and Eck fistula dogs, *Jr Exper Med*, 1937, lxxv, 455-467
- 36 Unpublished data This Laboratory
- 37 RALLI, E P Personal Communication
- 38 WAGREICH, H, ABRAMS, A, and HARROW, B Detoxication of benzoic acid by glucuronic acid in humans Rate of detoxication, *Proc Soc Exper Biol and Med*, 1940, xlv, 46-49
- 39 LIPSCHITZ, A, and BUEDING, E Mechanism of biological formation of conjugated glucuronic acids, *Jr Biol Chem*, 1939, cxlix, 333-358
- 40 WINTROBE, M M Relation of disease of the liver to anemia, type of anemia, response to treatment, and relation of type of anemia to histopathologic changes in liver, spleen, and bone marrow, *Arch Int Med*, 1936, lxvii, 289-306
- 41 WATSON, C J Studies on urobilinogen III The per diem excretion of urobilinogen in the common forms of jaundice and diseases of the liver, *Arch Int Med*, 1937, lxv, 206-231
- 42 BARKER, W H Excretion of bile pigment and hepatic functions in diseases of the blood, *Arch Int Med*, 1938, lxi, 222-246
- 43 WILDER, R M, and WILBUR, D E Diseases of metabolism and nutrition, review of certain recent contributions, *Arch Int Med*, 1938, lxi, 297-365

- 44 MESSINGER, W J, and HAWKINS, W B Arsphenamine liver injury modified by diet
Protein and carbohydrate protective, but fat injurious, *Am Jr Med Sci*, 1940, cxcix,
216-225
- 45 GOODMAN, L, and GILMAN, A Textbook of pharmacology, 1941, Macmillan, New
York, pp 137, 295
- 46 THOMPSON, W D, RAVDIN, I S, and FRANK, I L Effect of hypoproteinemia on wound
disruption, *Arch Surg*, 1938, xxxvi, 500-508
- 47 TAFFEL, M, and HARVEY, S C Effect of absolute and partial vitamin C deficiency on
healing of wounds, *Proc Soc Exper Biol and Med*, 1938, xxxviii, 518-525
- 48 BINKLEY, G, and PACK, G T Personal Experience
- 49 GOLDHAMMER, S M Liver extract therapy in cirrhosis of the liver, *Arch Int Med*,
1933, liii, 54-57
- 50 CASTLE, W B, and MINOT, G Pathological and clinical description of the anemias
1936, Oxford University Press, New York, pp 115-117

VITAMIN D IN THE TREATMENT OF INFECTIOUS ARTHRITIS *

By CHARLES H SLOCUMB, M D , *Rochester, Minnesota*

IN 1935 Dreyer and Reed ¹ reported clinical improvement among patients who had infectious (rheumatoid, atrophic) arthritis when treated with large doses of vitamin D. Reports which have appeared in the literature are summarized in table 1. Livingston ² reported that his best results were

TABLE I
Summary of Findings in the Literature Concerning Treatment with Vitamin D
in Cases of Infectious Arthritis

Investigators	Patients Treated with Vitamin D	Percentage with Clinical Improvement
Dreyer and Reed ¹	34	73.5
Vrtiak and Lang ⁵	20	60
Holbrook and Hill ⁶	25	20
Livingston ²	14	86
Wyatt, Hicks and Thompson ⁷	40	20
Farley ⁸	27	100
Steck ⁹	Not stated	75 to 80
Steinberg ¹⁰	29	34
Abrams and Bauer ³	18	44
Snyder and Squires ¹¹	13	69

from the combination of vitamin D therapy and fever therapy. Abrams and Bauer ³ seldom saw objective evidence of improvement accompany clinical improvement in their patients and observed that the beneficial effects of vitamin D were only transitory.

PROCEDURE

Fourteen patients with chronic infectious (rheumatoid, atrophic) arthritis were chosen for study. Their ages were from 17 to 59 years. The infectious arthritis had been present from seven months to seven years. For each patient conservative treatment had been tried, but it was inadequate in controlling the arthritis. Preparations of vitamin D used were "Viosterol—Experimental" (1,000,000 units per gram), a special solution of activated ergosterol, and a crystalline vitamin D in propylene glycol (40,000 U.S.P. units per gram). These were furnished, respectively, by Parke, Davis and Company, Mead Johnson and Company, and the Winthrop Chemical Company. The daily dosage varied from 52,500 units to 386,000 units. The administration of vitamin D was continued from twelve days to fifteen and a half months. If no clinical improvement occurred, its administration was continued for at least one and a half months. Each patient was studied during the administration of vitamin D in regard to subjective and objective

* Received for publication August 17, 1940

changes, clinical and laboratory evidence of toxicity, and the duration of improvement following discontinuance of the medication

Because of the marked variation of symptoms in infectious arthritis, several courses of treatment were given to some of the patients, to be as certain as possible that such improvement as was obtained was due to the vitamin D and not to spontaneous remissions. The 14 patients were given 25 periods of treatment with vitamin D. These patients have been followed for at least one year since the administration of vitamin D was discontinued.

Clinical improvement was evaluated on the basis of the information obtained from the patient in regard to pain, subjective stiffness, fatigue, limbering up, and the amount of aspirin required. Objective improvement was determined on the basis of swelling and tenderness of the joints.

RESULTS

Clinical improvement to the extent of disappearance of 25 to 75 per cent of symptoms occurred in seven patients (50 per cent), four (28.6 per cent) obtained no relief of symptoms, three (21.4 per cent) had partial relief of symptoms during one or more periods of treatment but did not improve during a subsequent trial of treatment with vitamin D.

The 14 patients were given a total of 25 periods of treatment. Eight treatments (32 per cent) resulted in no symptomatic relief, three treatments (12 per cent) resulted in subjective improvement to a degree of 25 per cent, twelve treatments (48 per cent) resulted in improvement to the extent of 50 per cent, and two (8 per cent) resulted in improvement to the extent of 75 per cent (table 2). Objective improvement was not noticed after 11

TABLE II

Effects of 25 Courses of Therapy with Vitamin D in 14 Cases of Infectious Arthritis

Treatment	Symptomatic Improvement		Vitamin D, units	
	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
25 courses	17	0	386,000	52,500
	0	8	315,000	80,000

treatments (44 per cent), objective improvement to the extent of 25 per cent was noticed after 12 treatments (48 per cent), and improvement to the extent of 50 per cent was noticed after two treatments (8 per cent). There was considerable variation in the readings of the sedimentation rate of erythrocytes and in the concentration of hemoglobin, improvement in these was very inconstant and frequently did not parallel the clinical and objective improvement.

There was no correlation between the amount of improvement and either the daily dose or the total dosage. When improvement occurred it was first

noticed from five days to three weeks after starting the administration of vitamin D

After the administration of vitamin D was discontinued, one patient maintained the improvement for one and a half years and another for two and a half years, before having a return of the active infectious arthritis. The other patients had a return of symptoms within eight days to two and a half months after administration of the vitamin D was discontinued. In most cases, the symptoms returned and were as severe as they were before vitamin D was given. Three of the patients had transitory exacerbations of the infectious arthritis while taking vitamin D, and in one case the infectious arthritis was more active after the administration of vitamin D was discontinued than when it was started.

The most frequent symptoms of toxicity from vitamin D were loss of appetite, the presence of a sweet taste in the mouth, nausea, vomiting, headache, polydipsia and polyuria. Twelve of the 14 patients had toxic symptoms in at least one period of treatment. Toxic symptoms occurred in 17 of the 25 periods of treatment (table 3).

TABLE III

Relation of Symptoms of Toxicity to Symptomatic Improvement and Daily Dosage during 25 Courses of Vitamin D in 14 Cases of Infectious Arthritis

Treatment	Symptoms of Toxicity		Symptomatic Improvement		Vitamin D Units	
	Present	Absent	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
25 courses	17 0	0 8	12 5	5 3	386,000 315,000	52,500 70,000

There was a higher percentage of improvement among those who had toxic symptoms than among those who did not, but it is obvious that toxic symptoms are not necessary to produce improvement, nor will doses of vitamin D sufficient to produce toxicity necessarily produce improvement in a case of infectious arthritis. Some patients tolerate very large doses of vitamin D and others react to small doses. It did appear that patients who had had toxic symptoms from vitamin D usually did not tolerate as much on subsequent trials without producing toxic symptoms.

Studies of the serum calcium were made during 15 of the 25 courses of treatment (table 4). Symptomatic improvement was experienced by all of the patients who had an elevation of serum calcium, but of four patients with a serum calcium of less than 11 mg per 100 cc two experienced improvement and two did not. It is not necessary to produce a high serum calcium in order to obtain improvement of the patient's condition, but such an elevation frequently occurs. Toxic symptoms may occur with or without an elevation of serum calcium and this elevation is no gauge of the toxicity of the vitamin D for the patient.

The blood urea was studied because of the known toxic effects of large

TABLE IV

Relation of Serum Calcium to Symptoms of Toxicity, Symptomatic Improvement and Daily Dosage during 15 Courses of Vitamin D in 11 of 14 Cases of Infectious Arthritis

Treatment	Serum Calcium		Symptoms of Toxicity		Symptomatic Improvement		Vitamin D, Units	
	More than 11 mg per 100 c c	Less than 11 mg per 100 c c	Present	Absent	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
15 courses	11	0	8	3	11	0	386,000	52,500
	0	4	4	0	2	2	210,500	140,000

TABLE V

Relation of Blood Urea to Serum Calcium, Symptoms of Toxicity, Symptomatic Improvement and Daily Dosage during 16 Courses of Vitamin D in 12 of 14 Cases of Infectious Arthritis

Treatment	Blood Urea		Serum Calcium		Symptoms of Toxicity		Symptomatic Improvement		Vitamin D, Units	
	More than 40 mg per 100 c c	Less than 40 mg per 100 c c	More than 11 mg per 100 c c	Less than 11 mg per 100 c c	Present	Absent	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
16 courses	6	0	4	0	5	1	6	0	386,000	105,000
	0	10	6	4	8	2	7	3	280,000	52,500

doses of vitamin D on the kidneys (table 5) ⁴ The level of blood urea was followed during 16 of the 25 periods of treatment with vitamin D Readings of more than 40 mg per 100 c c were found in six of the 16 periods of treatment All six of the patients with an elevated urea obtained some relief of symptoms and five had toxic symptoms to warn the patient to stop taking vitamin D However, one patient with a blood urea of 46 mg per 100 c c had no symptoms to warn him of the toxicity of the vitamin D for the kidneys By the time the concentration of urea was elevated, that of the serum calcium was also elevated A normal concentration of blood urea was not an indication that the patients would experience symptomatic improvement or symptoms of toxicity It is apparent that an elevated level of blood calcium is much more readily produced than is demonstrable damage to the kidneys Large doses of vitamin D may produce damage to the kidneys sufficient to elevate the blood urea In each case the concentration of urea returned to normal after administration of the vitamin D was discontinued

SUMMARY

Large doses of vitamin D have been of help in partially controlling the symptoms of infectious arthritis in seven of 14 patients and in 68 per cent of 25 courses of treatment Very little effect was seen on the objective

findings in the patients so treated. Vitamin D is not a specific agent for the control of infectious arthritis. Exacerbations may occur while the patient is taking large doses of vitamin D. The beneficial effects are only transitory, as a return of symptoms usually occurs after discontinuing its use. There is some risk of renal damage, which is apparently temporary if the administration of vitamin D is discontinued promptly after evidence of toxicity appears, but serious damage may occur. It is not necessary to produce toxic symptoms or renal damage to obtain clinical improvement.

There is no good correlation between clinical improvement and toxic symptoms or renal damage as evidenced by retention of urea. However, 11 patients who had an elevated concentration of blood calcium had clinical improvement and of four who had normal calcium, two experienced improvement and two did not.

Gastrointestinal upset was the most frequent sign of toxicity and usually gave adequate warning of the toxicity of the vitamin D, however, in one case the concentration of urea became elevated without the occurrence of any gastrointestinal upset. Patients receiving vitamin D should be watched carefully for symptoms of toxicity. Vitamin D therapy should be considered as one of many types of treatment which is sometimes of help in the temporary and partial control of symptoms of infectious arthritis. It is of very little, if any, use when lasting improvement is sought for the patient who has infectious arthritis.

The frequency of toxicity in this series is higher than has been reported in other series of patients treated with vitamin D. This may in part be due to other preparations being used by some of the other investigators.

REFERENCES

1. DREYER, I., and REED, C. I. The treatment of arthritis and massive doses of vitamin D, *Arch Phys Therap*, 1935, xvi, 537-540.
2. LIVINGSTON, S. K. Vitamin D and fever therapy in chronic arthritis, *Arch Phys Therap*, 1936, xvii, 704-706.
3. ABRAMS, N. R., and BAUER, WALTER. The treatment of rheumatoid arthritis with large doses of vitamin D, a critical evaluation, *Jr Am Med Assoc*, 1938, cxi, 1632-1639.
4. STECK, I. E., DEUTSCH, H., REED, C. I., and STRUCK, H. C. Further studies on intoxication with vitamin D, *ANN INT MED*, 1937, x, 951-964.
5. VRTIAK, E. G., and LANG, R. S. Observations on the treatment of chronic arthritis with vitamin D, *Jr Am Med Assoc*, 1936, cvi, 1162-1163.
6. HOLBROOK, W. P., and HILL, D. F. Treatment of atrophic arthritis, *Jr Am Med Assoc*, 1936, cvii, 34-38.
7. WYATT, B. L., HICKS, R. A., and THOMPSON, H. E. Massive doses of vitamin D in the treatment of proliferative arthritis, *ANN INT MED*, 1936, x, 534-536.
8. FARLEY, R. T. The management of arthritis, *Illinois Med Jr*, 1937, lxxi, 74-77.
9. STECK, I. E. Clinical experience in the treatment of arthritis with massive doses of vitamin D, *Illinois Med Jr*, 1937, lxxi, 243-248.
10. STEINBERG, C. L. Massive doses of vitamin D in chronic arthritis its effect on calcium metabolism, *Jl Lab and Clin Med*, 1938, xxiv, 17-24.
11. SNYDER, R. G., and SQUIRES, W. H. A preliminary report on activated ergosterol, *New York State Jr Med*, 1940, xl, 708-719.

MENTAL SYMPTOMS FOLLOWING CARBON DISULPHIDE ABSORPTION AND INTOXICATION *

By FRANCIS J BRACELAND, M D , F A C P , *Chicago, Illinois*

THE new therapeutic attack upon psychiatric conditions hitherto treated passively or empirically is a most encouraging development. The advent of new drugs and new methods, chemical, biological, and electrical, has changed the prognosis of mental disease and placed psychiatry in an enviable position, for it has progressed further in the past decade than many of its sister branches of medical science. As in all other branches of medicine, preventive measures play a most important part and the contributions of mental hygiene are of inestimable importance. We are beginning to recognize that there is a form of industrial mental hygiene the importance of which is as yet not completely appreciated. It merits our attention as this paper will demonstrate, and a careful survey of the mental health and mental hygiene measures in those industries with high morbidity rates would probably go far toward reducing the admissions to mental hospitals.

This paper is concerned with the results of the psychiatric examination of 120 workers employed in the viscose rayon industry. In the course of their daily work these individuals had been exposed to carbon disulphide fumes in varying intensity depending upon the department in which they were employed.

The occurrence of CS₂ poisoning and the opportunity for frequent contact with persons suffering from it are obviously small and limited to a few industrial centers. Despite the fact that exposure to carbon disulphide is a recognized industrial hazard, many experienced practitioners will never encounter its effects, and yet it cannot be said that a study of this kind is merely of academic importance. It reminds us of the necessity for questioning patients about their past and present occupation and of the importance of industrial hazards and occupational diseases. It would be most difficult to diagnose chronic CS₂ intoxication if the physician were not aware of the type of work his patient was doing.

CHEMICAL PROPERTIES OF CS₂

The disulphide or bisulphide of carbon is a colorless, transparent fluid of sweetish aromatic odor. When impure it smells like radishes. It boils

* Received for publication May 8, 1941.

From the Institute of the Pennsylvania Hospital.

This study was conducted under the auspices of the Department of Labor and Industry in the Commonwealth of Pennsylvania and directed by Dr F H Lewey of Philadelphia.

The literature abstracted above was selected. A complete list of references is appended to Bulletin No 46 of the Occupational Disease Prevention Division of the Department of Labor and Industry, Commonwealth of Pennsylvania. This bulletin is the report of a survey made by Dr F H Lewey and a group of specialists from the University of Pennsylvania Medical School.

at 104.8° F but volatilizes at room temperature. Mixed with air it is inflammable at 302° and if mixed with 20 parts by volume of atmospheric air it is highly explosive. Carbon disulphide shares this property with the group of gaseous anesthetics of which it is a member. Simpson, the famous Scottish surgeon who introduced chloroform into surgery and obstetrics, tested carbon disulphide as a narcotic years before it was used for any other purpose. Since Lewin's experiments in 1878 it has been recognized as a most severe neural poison probably because of its fat solvent properties. Its main avenue of entry into the body is through the lungs where it immediately permeates into the blood and is transported into the other organs including the brain. Its further course in the body is a matter of conjecture but we do know that 40 per cent of the carbon disulphide content of the blood disappears during the first hour after the worker leaves the poisonous atmosphere and 25 per cent additional during the second. It is eliminated in the urine and through the skin and lungs. The greatest part of the carbon disulphide inhaled is dissipated in the breath.

HISTORICAL DATA AND LITERATURE

In France, in the middle of the last century a new industry was introduced which used the sap of a tropical tree. Its resin, known to the French as caoutchouc and to the English as "India Rubber" arrived in Europe in the form of hard balls and had to be softened before it could be spread on canvas for use as rubber sheets manufactured into such articles as toy balloons. Carbon disulphide (CS_2), concerning whose poisonous qualities nothing was yet known, proved to be the best rubber solvent. The new rubberized fabric was a great success and a lucrative new trade was established in the home workshops of Paris. Here, in small rooms usually combined with living quarters, parents and children worked from morning until night in an atmosphere saturated with carbon disulphide vapors. Heating was costly, so none of the warm air was allowed to escape through the windows and the necessity for ventilation as a health measure had not yet been conceived.

In 1856, August Delpech,¹ a "public health minded" physician of the famous Bicêtre Hospital in Paris, published a report of 24 cases of carbon disulphide poisoning in "L'Union Medical," and in 1863 the report was extended to include 80 more cases. Delpech completely covered the entire scope of carbon disulphide intoxication in the fields of neurology, psychiatry and internal medicine, its prognosis, its industrial and sociological aspects so that only details could be added by later publications. He also fully described the case of one Victor Delacroix, aet 27, who in the course of his work was exposed to carbon disulphide fumes. He noted the extreme irritability and inexplicable rages evidenced by the patient, some of them leading to violence. He noted the sexual difficulties, the insomnia, bad dreams, and in fact described the whole toxic syndrome which we were to confirm independently 80 years later. As an interesting sidelight, he described the patient's son, a sweet-tempered lad who played in his father's

workshop, and who after three days' exposure to carbon disulphide gas became excited to the point of fury and attempted to attack and injure his father

For nearly 20 years after the original paper, the French literature had a monopoly on the subject. In 1881 Tamassia² reported from Italy the results of animal experiments with carbon disulphide. In 1884 Alexander Bruce³ described two typical cases of carbon disulphide intoxication from Edinburgh. In 1886 E. Mendel⁴ aroused the interest of the medical profession in Germany by exposing the dangers of carbon disulphide in the "cold" vulcanizing process.

Unfortunately through some mischance, the work of the great Charcot⁵ was responsible for beclouding the issue. In 1889 he presented a patient in his clinic whom he diagnosed as having "sulphide of carbon neurosis". The patient was hemiplegic, depressed and complained of terrifying dreams. Charcot stated that this was a form of hysteria but admitted that it was not the type which lends itself to hypnosis. He further stated that while some of the symptoms described by Delpuch were probably due to carbon disulphide vapors, most of them were due to hysteria. His contemporary, Marie,⁶ agreed with him and the bizarre findings were labeled hysteria. The opinions of these two masters threw other investigators off the track and remnants of their errors still remain in some places. Another controversial question arose, namely, is there such an entity as a true carbon disulphide psychosis or does the carbon disulphide merely act as a trigger which releases a latent psychosis in a predisposed individual? There was a great difference of opinion, due not so much to a contradiction of facts as to the differing basic conceptions of two antagonistic psychiatric schools.

Laudenheimer's⁷ monograph stressed the importance of carbon disulphide as an exogenous poison which might initiate a psychosis. However, he went too far and included some incurable forms of dementia in his group and attributed them to carbon disulphide. Bonhoeffer⁸ reported 14 cases of carbon disulphide psychosis, eight in rubber workers and six in viscose rayon workers. In the same report he examined critically Laudenheimer's cases and stated that five of them were typically toxic psychoses and the remainder were probably schizophrenic.

Laudenheimer's opponents went to the other extreme and ascribed to carbon disulphide the rôle of *agent provocateur* only. Today Bonhoeffer's thesis that there can be no doubt of the existence of a toxic psychosis due to carbon disulphide has won general acceptance and we hope to add further confirmation of it in this paper. In his monograph Bonhoeffer clearly defines the criteria by which a toxic psychosis can be diagnosed. He states that in toxic psychoses (which he calls amentia) the following characteristics can be noted. Early there is (1) clouded consciousness, (2) restlessness and very acute motor excitement, (3) hyperacuity of all senses especially optic, and, (4) increased emotionalism. Secondly, or as a consequence, there appears incoherence, perplexity and amnesia for the time of the psychosis.

Finally, there is an acute psychosis passing over into a chronic psychosis of the Korsakoff type. He felt that a diagnosis of toxic psychosis due to carbon disulphide intoxication should be made only on the basis of recovery after an illness which did not exceed several months or a year at most.

In America, Peterson⁹ in 1892 described three cases of mania which occurred in individuals who worked in the same room of a rubber factory and were exposed to carbon disulphide. All three patients recovered. In the same year, 1892, Bard¹⁰ reported two cases of acute mania in rubber workers. One patient killed a man whom he thought had wronged him and then destroyed himself. In 1904 and 1905 three cases of carbon disulphide intoxication in workers of "an artificial silk plant" were reported by Jump and Cruce,¹¹ and by Francine.¹² from the Hospital of the University of Pennsylvania. Francine's patient began to suffer almost from the first day of his employment. He slept poorly, lost his appetite and was exhilarated while in the factory and depressed when out of it. The night before he was taken to the hospital he had a peculiar attack during which he was confused, delirious and maniacal. This was most probably a case of acute carbon disulphide poisoning. The cases described by Jump and Cruce were examples of this chronic intoxication. One of them is described as being at first exhilarated and loquacious when he went to work in the churn room, later he became depressed, tactiturn, irritable, suffered from insomnia, memory defects and loss of sexual power.

Twenty years later, Dr. Alice Hamilton¹³ listed in her book, "Industrial Poisons in the United States," the risks of carbon disulphide intoxication in viscose rayon plants. From Holland, Kranenburg¹⁴ wrote on the subject in 1925, in 1928 Quarelli¹⁵ reported that almost 33 per cent of the viscose rayon workers in Torino developed Parkinsonism. The situation in America remained unchanged, however, until Dr. Alice Hamilton again raised her warning voice in 1937.

In 1938 Gordy and Trumper¹⁶ reported six cases which they had examined, three acute and three chronic, four women and two men. The symptom complex was practically the same as that noted by other workers. They state that one patient, a woman, had lilliputian and brobdignagian hallucinations and that this was the first time this had been chronicled in the literature. All of their cases were invalids.

METHOD OF EXAMINATION AND GENERAL CONSIDERATIONS

It should be noted that none of our patients was an invalid, they were all ambulatory and, with three exceptions, all were working. The psychiatric examinations were conducted by means of informal talks and the use of simple memory tests. Where the patient's mental ability was in question efforts were made to determine his approximate status. Usually the examiner was fortified by means of a questionnaire which had been filled out previous to the examination and which facilitated the work considerably.

Particular attention was paid to the spontaneous remarks of the patient and the approach was changed frequently in order to avoid the possibility of a worker's being prepared for the examination by those who had already been interviewed. Fortunately, it was possible for the psychiatrist to interview one-fourth of the group within 15 to 20 minutes after leaving their respective work rooms.

In addition to the patients examined, the records of all of the mental hospitals in the surrounding areas were also carefully gone over and particular attention was paid to anyone who had been exposed to carbon disulphide*. This was a herculean task, but it proved to be very much worth while, and later we will speak of the convincing indications of toxic psychoses which were unearthed.

THE ACUTE PSYCHOSES

In the routine examinations, three workers were seen who were definitely mentally ill at the time of the examination. All three were employed and two of them had come directly from work to the examining room. One man, aged 38, was led in by a fellow employee. He had been working in a part of the plant where the exposure was greatest. On the night of the examination the foreman had noticed that something was wrong and had transferred him to another department in which both the work and exposure to the gas were light. The patient was confused and disoriented, he complained of being "in a fog." He said he knew something was wrong, he had been nervous and irritable for several months but the condition was much worse in the past few weeks. He appeared more like a man of 50 years than 38 which he claimed to be. He complained of extreme irritability and rapid mood changes. He was unable to control the overwhelming impulse to anger—at home or in his shop. He had been unable to sleep more than two hours at a time, when he did sleep, it was broken and troubled and he dreamed of falling from great heights, of robberies, etc. At times he was "flighty and sleepy" during working hours, but he was covered and protected by the other men so that he would not lose his job.

His memory had been poor for months. He would go into stores and forget what he went for. At the time of the examination he could not recall the day or date. He could not repeat four digits after one minute. Several times during the examination he forgot the topic of conversation. Peculiarly enough, his memory for past events was good. He felt that the transfer would facilitate his return to health. He believed this was the second time that the gas had "gotten him." On the previous occasion, following his transfer to another department he had improved within a week or two.

He complained of complete loss of libido after a period of gradual lessening. He had become seclusive because he was not fit to be in the

* Credit should be given to Miss Lillian Erskine, formerly consulting expert of the Department of Labor. Her indefatigable work resulted in the breaking out of all of these case histories.

CARBON DISULPHIDE ABSORPTION AND INTOXICATION

company of others. He was sorry to be so angry and so wretched in his relationship with his family and fellow workmen.

The second patient presented the same type of picture with the addition of a definite hallucinosis of both the visual and auditory type. In addition to his psychotic findings the man had organic nervous signs and symptoms. In his hallucinations he could see the "spirit of a woman." He could travel great distances and explore foreign lands with a reality which convinced him. He could listen to the song of birds at times when no one could hear them. There was no evidence of dementia praecox nor of these hypnagogic hallucinations.

The third patient in question, a man of 42 years, showed more age than the others. He said his memory was so bad that he feared loss of mind. He was so irritable that he felt like killing his children and he had actually threatened to do so. He was bothered by terrifying visions which caused him to cry out and his wife would have to awaken him. He told his wife that time would tell what would happen to him—"with the work would kill him or he would end in an asylum." He added that he had worked 16 years in another plant and nothing like this had occurred that he had never even had an argument. He would "see things" at night and then would get scared when he realized they were hallucinations. There were also some vague paranoid ideas.

Five other patients who presented a severe toxic syndrome at the time of the examination gave evidence of previous psychotic episodes. So far as they had been confined in mental hospitals. One of the patients gave a history (which was later verified) of having upset the bed and thrown his wife on the floor, he urinated in the radiators, and became lost in his house which contained only four rooms. He was furloughed from the hospital and improved rapidly.

In evaluating the histories of the cases unearthed in the mental hospital we considered only those which were definite uncomplicated toxic psychosis in people who had been exposed to carbon disulphide at the onset of their illness. Many of them were taken ill while at work. One complicating factor occurred often, the patients' reactions were usually of the manic type and as a result, they would become loud, aggressive and combative, the general hospital was not equipped to handle them so they would be arrested and taken to the local jail. It usually took about three days to complete formalities for admission to the state mental hospital and on several occasions patients cleared up shortly after their arrival in the institution.

The following brief summary of one case exemplifies others which were selected as definite carbon disulphide psychoses.

Case 13 Male, aged 33, married. He was exposed to carbon disulphide for several months and eight days. No familial history of mental or nervous disease. He was admitted to the hospital handcuffed, ma

normal The pulse was 90 and the systolic blood pressure 120, diastolic 80 Other systemic examinations were negative The pupils were dilated The patellar reflexes were unequal—more active on the left side The Babinski sign was absent There was a fibrillary tremor of the tongue and slight tremor of the hands The Wassermann reaction was negative The urine showed traces of albumin and sugar He recovered quickly and thoroughly except for amnesia, the entire experience was lost and not regained He was paroled after several months and remained symptom free Immediately prior to his illness his wife had noticed that he was acting queerly—"voices began" and he "went around and around" He also showed the brobdignagian hallucinations mentioned by Goidy and Trumper in that he "felt taller than everyone"

This case is typical of the others except that recovery was more rapid The other nine patients discovered in mental hospitals recovered, in from two to four months, the longest taking six months and 21 days It is a notable fact that even though the patients became entirely clear mentally their memories remained poor

The following brief table gives a summary of the cases found in mental hospitals

TABLE I

	Age	Sex	Length of Exposure to CS ₂	Onset	Symptoms	Duration
Case 1	33	M	2 mo , 8 days	Acute	Violent, assaultive, hallucinated, delusional	3 days
Case 2	62	M	12 years	Acute	Resistive, assaultive, confused, grandiose	4 mo , 10 days
Case 3	24	F	7 years	Over 2 weeks	Hallucinated, maniacal, overactive, overtalkative, rapid mood change	6 mo , 21 days
Case 4	23	F	3 years	Acute	Confused, violent, profane, rambling, delusional	10 days
Case 5	27	M	5 weeks	Acute	Grandiose, excited, talkative, hallucinated	3½ mos
Case 6	30	M	Unknown	Acute	Violent, noisy, destructive, confused, delusional	Died of intercurrent infection
Case 7	39	M	5 years	Acute	Visual and auditory hallucinations, combative, delusional, suspicious	8 weeks
Case 8	50	M	3 years	Acute	Neurological signs, vomiting, giddiness, extreme nervousness	2½ years
Case 9	45	M	Unknown	Acute	Delusional, hallucinated, overactive, amnesia	4 months (relapsed later)
Case 10	53	M	Unknown	Gradual	Combative, depressed, delusional, amnesia	4 mo , 4 days

Usually the psychoses resulting from exposure to carbon disulphide are of the manic type with acute confusion, delirium and hallucinations The onset is generally acute but in many instances there is a gradual personality change manifesting itself to members of the patient's family or his friends

and fellow workmen. It is an insidious change and is noticed after varying periods of exposure to the gas. There is a phase of irritability accompanied by headache and insomnia and also a period of depression. The libido is markedly lessened or disappears entirely. Dreams of a terrifying nature frighten the patient and constant repetition of them, night after night, makes him reluctant to attempt to secure the meagre sleep which he needs so badly. The patients frequently become seclusive. The actual break may come while the patient is at work. An English report states that in one instance it was necessary to board up the windows of a factory to prevent maniacal patients from jumping out.

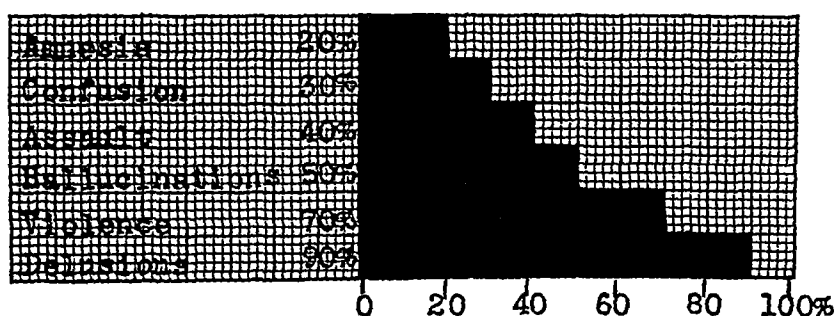


FIG 1 Incidence of symptoms in 10 psychotic patients Expressed in per cent

Rodenacker was of the opinion that carbon disulphide has a special affinity for individuals of the cyclothymic type. He also suggested that carbon disulphide psychosis was not per se a toxic psychosis but rather that it was an intoxication occurring during a maniacal or depressive phase. We are unable to subscribe to his theory. Our studies indicate that there is a carbon disulphide psychosis, that it is a definite clinical entity and it is of the toxic type. Rodenacker goes further and states that he believes the schizoid type of individual to be comparatively insensitive to carbon disulphide and describes one man of this type who felt well while exposed to carbon disulphide fumes in concentrations which caused discomfort to his fellow workmen. However, we saw several individuals of asthenic habitus and definite schizoid make-up who were adversely affected by the fumes. True enough, some of the patients felt better while in the carbon disulphide atmosphere but this was early in their exposure and it had no relationship to their body build.

The rôle of carbon disulphide as an "agent provocateur" will be considered at a later time. We have examined several patients in state hospitals who were diagnosed paranoid schizophrenia. One man was of particular interest. He had had a previous mental break years before while exposed to high concentrations of carbon disulphide. He recovered, was able to carry on his work and did very well until he was returned to the same department and the same high carbon disulphide concentration in which he became ill before. We are aware of the psychological hazard to the patient upon being returned to the department in which he and other workers had

become ill We also examined the records of other patients who had presented schizoid symptoms, and while we believe that carbon disulphide was the exciting cause of the attack, we are as yet unable to prove this statement

Altogether, we rejected 20 suspicious cases because of some complicating factor In five instances we felt that the data were insufficient Seven cases were discarded because of specific serologic findings One man had evidences of cerebral arteriosclerosis at the age of fifty One had a manic depressive history and three were schizoid personalities Three were discarded because the duration of the illness seemed too long for a carbon disulphide psychosis

CHRONIC ABSORPTION AND INTOXICATION

In order to facilitate the report we have divided the record of the non-psychotic patients into four groups They are designated by number and will be described later To avoid confusion of symptoms we completely rejected five workers because they had extraneous complications One of these had sustained a skull fracture in an automobile accident, two were chronic alcoholics, one had syphilis and one patient was 69 years of age It was thought wiser to reject these men than to try to separate out the symptoms Peculiarly enough, all five of the patients would have been classed under our mildest group The remaining workers are designated as follows

Group 0—Negative, no evidence of toxic symptoms

“ 1—Mildly affected

Group 2—Moderately affected

“ 3—Severely affected—toxic reaction

The negative group consisted of 14 workers They are regarded as negative from a psychiatric standpoint Their ages ranged from 28 to 53 years The shortest term of exposure was five and one-half years and the longest term 26 years Even though these patients had no definite symptoms they all complained of increased irritability Only two of the group had worked in the sections which were exposed to the gas in high concentrations One of the men who had worked in a mild exposure of carbon disulphide for 25 years was negative from a psychiatric standpoint but he presented some organic neurologic signs

Group 1 (Mildly Affected) There were 32 workers placed in this group The standards by which they were judged could not be rigidly defined The presence of one or several symptoms of toxicity in a mild form qualified the patients for admission to this group While many of the complaints were apparently mild at the time of examination, they did not augur well for the future One worker complained that he “got burnt up” very quickly and that he had engaged in numerous quarrels This is seemingly not very serious but this patient was perplexed by his conduct, he had never acted this way before He was afraid that if it had continued he

would have killed a man. He was laid off from work and after he had been out for one week, his disposition improved, he became more gentle and friendly and got along better with his family than he had for years. Another worker, in this same group, had been formerly nicknamed "Happy", at the time of his examination he stated that this was a sad misnomer, he was depressed because of his irritability and quarrelsomeness. The same man complained of terrifying dreams of snakes and horrible things such as robberies and "killings". He stated that at times when he retired his body would seem so light that it would float away from him. He would have at times—"a dream within a dream," i.e. he knew he was dreaming and hoped his wife would awaken him as he was powerless to help himself.

In two of the cases examined in this group the workers were believed to be low grade morons and not too much significance was attached to their subjective complaints.

The following examples are typical of this group.

Case 1 Male, aged 25. He had been employed for four and three-quarters years. The change of personality had been noted by others as he had become restless, easily excitable, and irritable. He would get a "funny leery feeling," was apathetic and easily fatigued. He slept little and poorly. During sleep he had sensations of falling. He had beginning paranoid ideas about fellow workers. He would get sick after being off for two days, but as soon as he got back into the fumes he felt better. His libido was diminished. He has since been laid off for two months and gained 20 pounds. Once before when out on strike for nine months he gained 40 pounds. He also has other medical complaints.

Case 2 Male, aged 31. There had been heavy exposure for approximately four years. He felt that he was a nervous man, being fidgety—and restless. His sleep was interrupted, sometimes for weeks at a time he would get very little sleep at all. He was not worried about anything but would simply lie awake and think about irrelevant things. He dreamt about things which frightened him, and jerked in his sleep. He frequently became depressed and was at a loss to understand why, because "things were running smoothly enough." His memory had been fairly good but if he got excited he became confused. His "mind wandered" more than it did before.

Group 2 (Moderately Affected) Twenty-five patients were placed in this group. The symptoms presented here are more pronounced but are still not serious enough to be considered a definite "toxic reaction." Sixty-four per cent of these patients complained of memory defect about which more will be said later on. Only two of the 25 patients were churn room workers (supposedly the location of the greatest carbon disulphide exposure) while the remainder were spinners and workers at miscellaneous jobs. Typical cases of this group follow.

Case 3 Patient, 32 years old, male. Exposure was moderate. He had four children, and had been 11 years with present company. He had been getting increasingly irritable and angry for about the last six years. "Things get on his nerves." He tosses about all night in his attempts to sleep and sleeps one hour at a time. He has bad dreams occasionally. He was sick and was off duty for four weeks and at the end of this time he felt well. Once he had ten days' vacation and on the sixth day felt perfectly well. He states that the "fumes don't agree with him." His memory

used to be good but it is poor now. He loses and forgets things. He was formerly interested in his home. Now he has lost interest and just does nothing. His libido has become markedly decreased. He believes that if he could just get one good night's sleep, he would feel much better.

Case 4 Male, aged 37. Mild exposure during 16 years' employment by a viscose company. He complains that he is irritable and mean with his wife and children. Formerly he had real hard work with another company but was never like this. He rolls and tosses all night. He sleeps 15 minutes and thinks it has been eight hours. He has frightful dreams, gets scared and gets up to examine the doors and windows. At times he has gotten up out of bed and called out of the window, was afraid someone was after him. There is a marked change in his personality. His memory has noticeably "gone bad." He goes to night school—takes courses and tries to advance himself, but it seems to be impossible. His libido has been lessening for the last seven years. The last two years it has been especially bad. Marital relationship is no longer pleasurable—it is a task. He has neither the desire nor ability to accomplish sexual relationships. He was formerly interested in an avocation but he has now given it up because of apathy.

Group 3 The Toxic Reaction (Severely Affected) This group includes twenty-one workers. All gave evidence of a toxic process and all of them had been exposed to varying concentrations of carbon disulphide. They were recruited from two factories widely separated and in both places insufficient attention had been paid to industrial hygiene and preventive measures. At this point we should again call attention to the fact that the patients presented many additional symptoms, referable to all other bodily symptoms but in this paper we are simply reviewing those which come under the domain of psychiatry. Several examples of this group have been abstracted and presented below.

Case 5 Male, aged 36. He is prematurely aged and gives the appearance of 55. He has been at this type of work for 10 years and has been under heavy exposure for last three years. He is more irritable than ever before and is worse at night ("You can go back over my record at home, I was formerly easy going—now I can't take it, I am ready to fight everybody"). His wife says he is losing his mind—"is forever angry and arguing." He can hardly get himself to sleep. He awakens after one hour and thinks the whole night has passed. He jerks so badly that children had to be removed from the bedroom in his small house. His dreams are bad, of fights, killings, etc. He fights and groans and gets scared. His memory is bad. "If you send me to the postoffice, I might get there and might not. I used to have a good memory, can remember things in my boyhood but almost forget this morning." His interest is narrowing and he has no energy. He gets as tired as a man of seventy. His libido is gone, the change beginning months ago. He hears "people hollering" and when he looks there is no one there. He has optical illusions while at work and these illusions are concerned with the churns. "I was never a nervous man before. I never took a pill till nine months ago—since then I have taken enough to kill all the people around town."

Case 6 Male, aged 34. Although exposed for 13 years, he feels that he was mild tempered up until one year ago. Now he is so irritable and angry at home that his wife says he is one of the meanest men who ever lived. He is ashamed and worried about this. He is terribly fatigued upon retiring but after three hours' sleep bounds out of bed fully awake. He does not understand this. He has many bad dreams, about fire, falling, running away, etc. He is now very much afraid because

recently he was so angry that he wanted to kill his wife. This scared him and he wants to do something about it. The two years he was out of the plant he felt like a normal person. He fears running into things as he walks. He has seen horrible, grotesque faces and he was so frightened that he said his prayers! With his eyes open or shut he saw these faces. His libido is markedly lessened. When he attempts intercourse (infrequently) he fails miserably.

It was apparent from analysis of this group that a definite toxic syndrome presented itself. It consisted of the following symptoms which were fairly constant: (1) Personality change (always for the worse), (2) marked irritability, (3) memory defect, (4) insomnia, (5) bad dreams, (6) lessening of libido, and (7) constant fatigue.

TABLE II
Percentage of Incidence of Psychic Symptoms in 78 Viscose Rayon Workers,
Subdivided into Three Groups of Severity

Grade of Severity	Actual Number of Members in each Group	Change of Personality	Memory Defect	Marked Irritability	Lessening of Libido*	Insomnia	Bad Dreams	Marked Fatigue†	Hallucinations	Delusions	Depression	Confusion
I	(32)	40.5	31.5	43.6	43.6 ¹	40.5	37.5	31.5 ²	4.1	0	0	0
II	(25)	52	64	56	36	44	44	12	12	4	8	8
III	(21)	90.1	86	81	66.8	62	57	47.5	23.8	23.8	23.8	14.3
I-III <i>r</i>	(78)	58 +0.97	56.5 +0.96	58 +0.98	47.5 +0.72	47.5 +0.93	45 +0.98	29.5	11.6 +0.995	7.7	9	6.4

* The comparatively smaller number of workers in this group may be caused by the fact that in order to avoid error, men over 40 years of age were not considered, this increased the sampling error.

† Another sampling error was detected. In one group the question about fatigue was omitted.

Table 2 indicates that the frequency of psychic symptoms increased with the severity of carbon disulphide absorption. This is confirmed by the correlation coefficient (*r*) strongly suggesting an upward trend in all columns. Statistical significance cannot be attached to only one column: hallucinations, $r = 0.995$, $P = 0.06$.

The average number of psychic symptoms amounted to 2.7 in Group 1, to 3.3 in Group 2, and 5.8 in Group 3.

TABLE III
Percentage in Which Churn Room Workers, Spinners and Workers in Miscellaneous
Viscose Departments Shared in the Three Groups of Severity

Groups of Severity	I	II	III
Churn Room	31.2	8	57
Spinning Room	59.4	72	38.2
Miscellaneous Rooms	9.4	20	4.8

The group of the spinning room workers contributed more than one-half to the mild cases and almost three-fourths to the moderately severe cases but only somewhat over one-third to the severe cases. The churn room workers, correspondingly, represented not fully one-third of the mild cases but over one-half of the severe ones. One-fifth of the members of Group 2 consisted of workers of odd jobs such as pipe fitters, filter press cleaners and engineers who are sometimes very much exposed to fumes.

THE INDIVIDUAL SYMPTOMS

Regarding the irritability and anger little more can be said. They were recognized by the workers' family and colleagues and regarded seriously. During these phases the patient was left severely alone. The outbreaks of anger are usually short lived and are followed by a feeling of abject penitence during which time the patient frequently cries and complains that he is powerless to help himself. At times the rage assumes serious proportions and we noted several instances in which they were contributing factors toward broken homes. A general practitioner who was in no way connected with this survey informed us that the conduct of the people who lived in houses close to the mill, which were permeated by odors from it, was of an entirely different type from that of those who lived out in the country. He had observed them for several years and he felt that their conduct was characterized by lack of inhibition. Quarrels were frequent and marital difficulties marked. It can be noted that some of the earlier writers felt that lack of inhibition was one of the most frequent early signs of carbon disulphide intoxication.

Regarding the memory defects, when the subject was introduced it frequently brought immediate and emphatic response. Usually it was introduced by the worker himself. This was the more remarkable when it is remembered that many of the workers had not yet attained their fortieth year. It seems as though the memory loss was particularly for recent events, although this will have to be substantiated by further examination. Coupled with a progressive narrowing of interest and some arteriosclerosis plus the premature appearance of age in a portion of this group, it requires further study. Some of the spontaneous remarks about memory defects would have been amusing had they not been pathetic. One man had forgotten where he parked his car and was forced to wander about in a small town looking for it. A complicating factor was that his wife was in it. (We are aware of the possible analytical significance of this.) Another man had to be removed from the churn room because he could not remember the time of the charges. When some of the men were sent to the store for more than two items it was necessary to write them down. Several remarked significantly that if they were sent out for three things they would be bound to forget one of them. The constant complaint of loss of memory for names was disregarded because of its universality, but findings such as the one which follows cannot be disregarded. One man being questioned about his memory remarked, "Memory. You have me there. It started to go back on me on my first time in heavy exposure to the gas. I have to ask my wife what day it is. I used to have a good memory—I was noted for it, but no more." This patient failed to memorize three written digits in a period of three to five minutes as did four other patients. Approximate dates of illnesses, vacations, strikes, etc., which would ordinarily be retained were lost to some of the men. Some remarked that when they were off from work for a long period of time their memories improved.

A large percentage of the men complained of sleep disturbances. These were frequently difficult to evaluate because they were on "shift work" and those who had worked at night would have difficulty in sleeping during the day. This particular complaint is not confined to these workers and might be found in other men who worked on night shifts. Even allowing for this, however, there were definite changes in the sleep rhythm. Almost without exception the men complained of excessive fatigue and yet their sleep was broken and meagre. The two exceptions to this complained of a constant overwhelming desire to sleep and one had to be awakened during his meals. One curious fact was noted. Most of the men stated that if they fell asleep for 15 or 30 minutes they would awaken feeling as if they had slept five or six hours, without being refreshed. Two phenomena contributed to the broken sleep, one was "jerking" and the other was bad dreams. The first mentioned varied in intensity and some only became aware of it because their wives had so informed them. Others complained that the jerks were so marked and so sudden that they were awakened by them and the most severe cases were at times almost jolted out of bed. No one of the 110 men examined had dreamt of pleasant things. Some few did not dream at all and the remainder dreamt either of work or of horrible things. Mostly they were concerned with murders, suicides, falling from high places and fights. One man on the night before the examination dreamt that someone had pulled all of his teeth out. These observations agree in substance with the findings of other writers.

Some authors have stated that in carbon disulphide intoxication the libido is increased at first and only after continued exposure does it become lessened. While we searchingly questioned all of the workers we were unable sharply to demarcate these periods and men who had been exposed for a number of years stoutly denied interference with this function while others whose tenure was relatively short were apparently greatly affected. This recalls the two cases reported by James Ross in whom sexual function was lost after three weeks' exposure to the fumes. In two of our cases this change contributed to the separation of man and wife, while one man still in his twenties complained that because of his loss his wife had accused him of infidelity. In order to obviate any possibility of the age factor complicating our statistics we set 40 years as the arbitrary figure above which we would not consider loss of sexual power unusual, this figure is eminently fair and far below the normal age level for loss of libido.

It is impossible to explain the symptoms listed above as evidences of mass hysteria. True enough, there are instances of hysteria being found among these workers the same as in any large group. Our findings corroborate the findings of other investigators in foreign lands. Many of the men who have been mentioned here also had other measurable physical signs. As the final and deciding factor, the results of our animal experimentation leave no room for doubt, they are conclusive. These results have already been published.¹⁷

CONCLUSIONS

1 Acute carbon disulphide intoxication is comparable to the narcotic effects of other gaseous anesthetics

Chronic carbon disulphide absorption is associated with the physical changes described by Lewey and attributed to liver damage and subsequent vitamin B deficiency

2 Our survey convinces us that there can be no doubt of the existence of a toxic psychosis due to carbon disulphide

3 In the carbon disulphide psychoses the following characteristics were noted confusion, combativeness, hallucinations, delusions, depression, and finally, amnesia for the acute attack

4 While the onset of the psychosis is usually acute, a gradual personality change has also been noted by attentive observers This change is insidious and is accompanied by a phase of irritability, depression, headache and insomnia The libido is lessened, and dreams of a terrifying nature occur The break frequently comes while the patient is at work

5 It is probable that carbon disulphide also acts as an *agent provocateur* in individuals who are already predisposed to mental illness

6 A larger group of workers display a chronic form of absorption and intoxication symptoms Apparently these symptoms are not dependent upon physical habitus or heavy exposure to the gas but rather to individual susceptibility to carbon disulphide

7 The toxic syndrome consists of the following symptoms which are fairly constant Personality changes (always for the worse), marked irritability, memory defect, insomnia, bad dreams, lessening of libido and constant fatigue

8 It is apparent that once an individual has shown evidence of any toxic symptoms he should be removed from further exposure to carbon disulphide and never again be subjected to it in large quantities or in heavy concentrations

9 It is essential that a vitamin rich diet be procurable in the cafeterias and homes of the workers in carbon disulphide

BIBLIOGRAPHY

- 1 DELPECH, A Notes sur les accidents qui développent, chez les ouvriers en caoutchouc, l'inhalation du CS₂ en vapeur, *Gaz, hebdomadaire de médecine et de chirurgie*, 1856, III, 40
- DELPECH, A Accidents qui développent, chez les ouvriers en caoutchouc, l'inhalation du CS₂ en vapeur, *Union médicale*, 1856, X, 265
- DELPECH, A Expériences sur les animaux, *Gaz hebdomadaire de médecine et de chirurgie*, 1856, III, 384
- DELPECH, A Nouvelles recherches sur l'intoxication spécifique qui détermine le CS₂, *Annales d'Hygiène*, 2e Série, 1863, LXV, 65
- 2 TAMASSIA, A Del intossicazione acutissima, *Rivista sperimentale di freniatria*, 1881, VII, 20
- 3 BRUCE, A Chronic poisoning by CS₂, *Edinburgh Medical Journal*, 1884, XXIX, 1009
- 4 MEYDEL, E Vorstellung eines Kranken mit CS₂ Vergiftung, *Berlin klinische Wochenschrift*, 1886, XXXIII, 503
- MEYDEL, E Zur Lehre von der CS₂ Vergiftung, *Berlin klinische Wochenschrift*, 1901, LXXVIII, 783

CARBON DISULPHIDE ABSORPTION AND INTOXICATION

- 5 CHARCOT, H C Leçons du mardi, 1889, Lecrosnier et Babe, Paris
- 6 MARIE, P CS₂ et hystérie, Bull et mém Soc méd d hôp de Paris
- 7 LAUDENHEIMER, R Die Schwefelkohlenstoffvergiftung der Gummibäume, Leipzig
- 8 BONHOFFER, K. Ueber die neurologischen und psychischen Folgen der CS₂ Vergiftung, Monatsschr f Psychiat u Neurol, 1930, lxxv, 195
- 9 PETERSON, F Three cases of acute mania from inhaling CS₂, Boston Med Surg J, 1892, cxlii, 325
- 10 BARD, C L Insanity due to CS₂, South California Pract, 1892, v, 193
- 11 JUMP, H D, and CRUCE, J M Chronic poisoning from CS₂, J Am Med Bull, 1904, xvii, 193
- 12 FRANCINE, A P Acute CS₂ poisoning, Am Med, 1905, ix, 871
- 13 HAMILTON, A Industrial poisons in the United States, 1925, Macmillan, New York
- 14 KRANENBURG, W R H, and KESSENER, H H₂S und CS₂ Vergiftungen, Gewerbehyg, 1925, xii, 348
- 15 QUARELLI, G L'intossicazione professionale da CS₂ Bericht d. k. k. Hof- u. Landes-berufskrankh., Budapest, 1938
- 16 GORDY, S T, and TRUMPER, M CS₂ poisoning with a report of six cases, J Am Assoc, 1938, cx, 1543
- 17 LEWEY, F H, et al Experimental chronic carbon disulphide poisoning, Indust Hyg, 1941, xxi (Nov)

SULFANILAMIDE IN THE TREATMENT OF ERYSIPELAS *

By LAWRENCE S SIEGEL, M D , LEON ROSOVE, M D , and ALBERT G
BOWER, M D , F A C P , *Los Angeles, California*

PRIOR to the use of sulfanilamide in the treatment of erysipelas, there was no effective mode of therapy. Early in 1935 Myer-Heine and Huguenin¹ treated 150 cases with the dye sulphamido-chrysoidin, reporting rapid and constant results as regard temperature and local phenomena. Kramer² in April 1936 reported 32 cases treated with prontosil, and expressed the opinion that it was the most effective drug used against the disease. Breen and Taylor³ in June 1937 reported a series of 46 consecutive cases treated with prontosil in which the temperature fell to normal or below in 48 hours, and no spread or relapse occurred in any patient while taking the drug. Snodgrass, Anderson, et al^{4, 5, 6} conclude from a series of cases that sulfanilamide showed much better results than ultraviolet therapy in respect to the curtailment of the duration of the spread of the local lesion, of toxemia, and of the primary pyrexia. In a special report from the Herman Kiefer Hospital, in Detroit, in September 1938, Top and Young⁷ compare an equal number of cases, 80 in each series, treated with anti-sera and sulfanilamide and conclude that anti-sera are of no material aid in the treatment of erysipelas. With sulfanilamide the temperature fell to normal within two days as compared to six and one half days with anti-sera, and the proportion of sulfanilamide cases which showed no spread was double that observed with serum treatment. The average hospital stay with sulfanilamide treatment was seven days compared to 14 days in serum treated cases. Nelson, Rinzler, and Kelsey⁸ at the Bellevue Hospital treated 344 patients with sulfanilamide from January to July 1937, reporting an average of 6.8 days for the hospital stay. Hoyne, Wolfe, and Prim⁹ at the Cook County Hospital reported on the treatment of 998 erysipelas patients from 1934 to 1938. Eight hundred and twenty cases were treated with various remedies with a mortality of 11.4 per cent as compared with 168 cases treated with sulfanilamide with a mortality of 2.46 per cent. The authors conclude that sulfanilamide is the most effective form of therapy thus far used in the treatment of erysipelas.

Beginning April 1937, all patients with erysipelas entering the communicable disease unit of the Los Angeles County Hospital were treated with sulfanilamide. From April 1, 1937 to August 1, 1939, 303 patients with erysipelas were treated. The average number of days of illness before admission was 2.6 days. The precipitating factor was determined in 37 per cent of the cases as listed in table 1, trauma, furuncles, and ulcers were the most common. Seventy per cent of the cases occurred between the months

* Received for publication June 11, 1940

TABLE I
Erysipelas Showing Incidence of Precipitating Factors in 303 Cases

Precipitating Factors	Cases	Per Cent
Unknown	193	63.7
Trauma	30	9.9
Furuncle	20	6.6
Ulcers	15	4.9
Abrasions	7	2.3
Impetigo	6	1.9
Burns	5	1.6
Lacerations	4	1.3
Amputations	3	.9
Otitis media	3	.9
Mastoidectomy	3	.9
Miscellaneous	14	4.6
Totals	303	100

of October and March. The age incidence in table 2 shows that 11 cases occurred under one year of age, 20 cases between the ages of 1 and 4 years, and 39 cases after the age of 65 years. The sex distribution for all age groups was approximately equal. Sixteen per cent of the cases had one or more previous attacks. Graph 1 shows the distribution of areas involved,

TABLE II
Erysipelas Showing Incidence and Mortality Rates by Age Groups

Age Groups in Years	Males			Females			Totals		
	Cases	Deaths	Fatality Rate Per Cent	Cases	Deaths	Fatality Rate Per Cent	Cases	Deaths	Fatality Rate Per Cent
Under 6 Mon	3	1	33.3	3	0	0	6	1	16.6
6 Mon -1 Yr	1	0	0	4	0	0	5	0	0
1	3	0	0	7	0	0	10	0	0
2	2	0	0	4	0	0	6	0	0
3	2	0	0	2	0	0	4	0	0
4	1	0	0	2	0	0	3	0	0
5-9	3	0	0	6	0	0	9	0	0
10-14	4	0	0	1	0	0	5	0	0
15-19	4	0	0	4	0	0	8	0	0
20-24	3	0	0	5	0	0	8	0	0
25-29	13	0	0	5	0	0	18	0	0
30-34	8	0	0	12	0	0	20	0	0
35-39	7	0	0	12	1	18.3	19	1	5.3
40-44	13	0	0	11	0	0	24	0	0
45-49	19	0	0	13	0	0	32	0	0
50-54	11	2	18.2	10	0	0	21	2	9.5
55-59	17	0	0	22	0	0	39	0	0
60-64	14	0	0	13	0	0	27	0	0
65-69	11	0	0	8	0	0	19	0	0
70-74	4	0	0	5	0	0	9	0	0
75-79	2	0	0	1	0	0	3	0	0
80+	4	0	0	4	0	0	8	0	0
Totals	149	3	2.0	154	1	0.66	303	4	1.3

51 per cent were of the facial variety, 30 per cent occurred in the lower extremities, and 19 per cent were elsewhere. The severity of the illness was classified according to the initial temperature on admission. Thirty-nine and six-tenths per cent of the cases with a temperature up to 101° were considered mild, 39.2 per cent of the cases with a temperature from 101 to 103° F were moderately ill, 20.4 per cent of the cases with a temperature between 103 and 105° were severely ill, and 0.8 per cent of the cases had a temperature over 105° . One hundred and fifty-three cases had one or more associated diseases on admission as listed in table 3. Two hundred and

TABLE III

Erysipelas Showing Associated Conditions Present in 153 Patients on Admission

Associated Condition	Cases	Percentage Distribution of Totals
Hypertension	46	15.1
Atherosclerotic Heart Disease		
Infections of the Upper Respiratory Tract	38	12.5
Syphilis	22	7.3
Carcinoma	11	3.6
Varicose Ulcers Legs	9	2.8
Chronic Alcoholism	7	2.3
Diabetes	6	1.9
Pulmonary Tuberculosis	4	1.3
Miscellaneous Conditions	77	25.4

forty cases had white blood counts on admission, the average being 12,350 with 70 per cent polymorphonuclears.

In the treatment of erysipelas with sulfanilamide the dosage was calculated as follows. For children up to five years of age, one grain per pound of body weight for 24 hours was given. One half of the total dose was given at once and the other half was given in divided doses every four hours over the remaining 24 hours. The tablets were crushed and given in food or drink. If the drug could not be given by mouth because of vomiting or the condition of the patient, it was given subcutaneously in a 1 per cent solution in normal saline every six hours. When the drug was given by mouth, steps were taken to prevent acidosis. When given by hypodermoclysis in the 1 per cent solution, 10 c c of $\frac{1}{4}$ molar solution sodium lactate were added to each 100 c c sulfanilamide solution.* After 24 hours, the calculated dos-

* In 1937 the hospital laboratory carried out some experiments to determine whether or not sulfanilamide would remain stable when autoclaved. Since that time we have autoclaved all our sulfanilamide solutions for 20 minutes at 15 pounds pressure. We usually make up 100 liters at a time in single liter bottles, dissolving the drug in normal saline solution to which has been added sufficient sodium lactate to represent 100 c c of a $\frac{1}{4}$ M solution (of sodium lactate) in each liter. We have observed solutions made in this fashion for as long as 12 months, and find that they remain stable and unchanged. However, at room temperature some of the drug will crystallize out over long periods of time. This is effectively overcome by setting the flasks in hot water until it redissolves. We have also used 50 c c of either lactated Ringer's solution or Hartman's solution per liter in place of sodium lactate. The sulfanilamide may be made up in an $\frac{1}{40}$ per cent solution, and if a pure grade of drug be used this will not precipitate out at ordinary temperatures. We see

age for the previous 24 hours was reduced one-third, and on the third day an additional reduction to one-half of the initial dosage was made. This maintenance dosage was given for three to five days after clinical cure to prevent relapse. In older children and adults the plan of treatment was

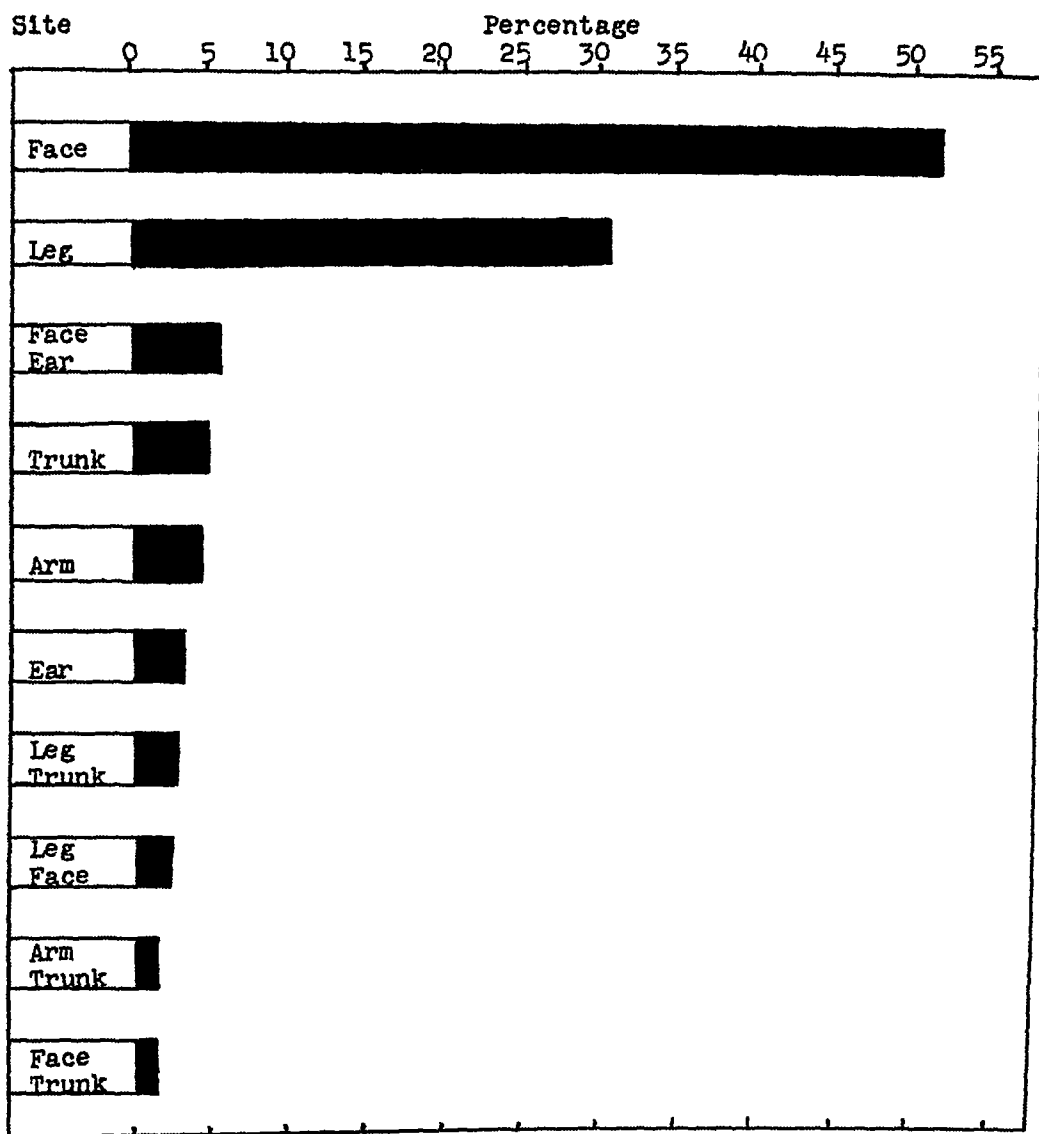


FIG 1 Erysipelas showing percentage distribution of areas involved in 303 cases

similar to that used in the younger age group, except the dosage was calculated at 15 grains for 20 pounds of body weight for 24 hours.

no particular advantage in the use of this latter solution, however, preferring to use the 1 per cent, because of the ease with which one can calculate the total amount of the drug given.

We have recently treated a number of cases of erysipelas with continuous wet compresses of a saturated solution of sulfanilamide and in a few other cases applied 2 per cent sulfanilamide ointment with gratifying results. The lesions regressed within 24 to 48 hours, although it was necessary to add oral sulfanilamide in some cases that did not respond adequately to local therapy. Traces of sulfanilamide were found in blood determinations following local treatment. The results indicate that local applications are of definite curative value, if, however, the lesions are extensive, oral sulfanilamide in addition is indicated.

Determinations of the sulfanilamide level in the blood were done in 121 cases. Ninety-four per cent of the determinations were taken 48 hours or more after admission. The average for the series was 5.8 mg per 100 c.c.

TABLE IV

Erysipelas Showing Relationship of Sulfanilamide Level to Duration of Fever in 121 Cases

Number of Hours Elapsed between Admission and Blood Specimens	Number of Specimens Taken	Average Blood Level in mg /100 c.c.	Number of Patients Whose Temperature Became Normal at Period Noted		No Effect on Temperature	
			Number Cases	Per Cent Dist	Number Cases	Per Cent Dist
6	2	3.5	0	0	2	100
12	2	4.3	0	0	2	100
18	4	5.0	0	0	4	100
24	13	4.5	4	31	9	69
48	43	5.5	22	51	21	49
72	40	6.3	24	60	16	40
72+	66	6.6	62	95	4	5
Totals	170	5.8	112	64	58	36

Table 4 shows the relation of the blood level to the duration of fever. The only conclusion we could draw from our series was that the concentration of the drug in the blood in this disease need not necessarily be high to be effective.

TABLE V

Erysipelas Showing Results in 303 Cases Treated with Sulfanilamide

Age Groups in Years	Average Hospital Period in Days	Average Duration in Hours of Fever	Average Period in Hours Required for Lesions to Regress
Under 6 Months	8	48	62
6 Mos -1 Yr	11	52	48
1	12	50	43
2	7	52	38
3	6	32	48
4	5	44	51
5-9	9	63	45
10-14	6	27	34
15-19	8	38	83
20-24	8	74	58
25-29	4	31	46
30-34	7	71	45
35-39	8	47	57
40-44	8	54	51
45-49	7	50	56
50-54	6	36	45
55-59	7	48	47
60-64	7	33	50
65-69	8	44	51
70-74	9	57	46
75-79	7	60	48
80+	10	38	48
General Average	8	48	50

In table 5 are shown the results of sulfanilamide therapy in erysipelas. The average period of hospitalization was eight days for all patients treated, and was approximately the same for all age groups with the exception of the ages between six months to one year in which it was 11 days, and the age group between one to two years in which it was 12 days. The average time required for the temperature to reach normal was 48 hours for all groups of patients treated except in the age group between 20 and 24 years in which it was 74 hours, and in the age group between 30 and 34 in which it was 71 hours. In 71.4 per cent of the cases the temperature dropped to normal in 72 hours. The average time required for the lesion to regress was 50 hours for all patients treated, and this was approximately the average for all age groups except in the age group between 15 and 19 years in which it was 83 hours. There was no spread of the lesion in any case, and only one case in the entire series had a recurrence of the lesion.

Complications of erysipelas were as follows: Abscess formation, eight cases, pneumonia with hemolytic staphylococcus septicemia and lung abscess, one case, and nephritis with uremia, one case. The total complication rate was 0.3 per cent.

Toxic reactions attributable to the drug were as follows: marked cyanosis in 11 cases, marked nausea and vomiting in nine cases, in five cases, rashes which cleared up promptly when the drug was discontinued, temporary psychosis in five cases, in three of which it subsided when the dosage of the drug was reduced, and in two patients, only when the drug was discontinued, severe secondary anemias in two cases, which cleared up with discontinuation of the drug and institution of iron therapy, hemolytic anemia in two cases, 72 hours and 96 hours after treatment was started, both of which proved fatal, toxic hepatitis and nephritis in one case on the fifth day of treatment, which responded to treatment consisting of a blood transfusion and intravenous glucose.

Prior to the use of sulfanilamide in the treatment of erysipelas the mortality remained very high with the various methods of therapy. Dr L. E. Sloan¹⁰ reviewed 882 cases of erysipelas treated with various remedies at the Los Angeles County Hospital from 1929 to 1933 and found a mortality rate of 32.9 per cent in infants under one year of age, and an average mortality of 8.1 per cent. This mortality rate was approximately the same as those reported in large series of cases by other authors.¹¹ There were four deaths in this series, as seen in table 2, or a gross mortality rate of 1.3 per cent. One occurred in a male infant, 21 days old, as a toxic effect of the drug, an acute hemolytic anemia developing on the fourth day of treatment. The usual treatment with blood transfusions was used without avail. One patient, a female aged 37, developed a hemolytic staphylococcus septicemia while under treatment, with resultant lung abscess, which was proved at autopsy. One patient, a male aged 53, developed toxic nephritis with uremia on the third day of treatment. One patient, a male aged 54, developed acute

hemolytic anemia on the third day of treatment. The drug was immediately discontinued and three blood transfusions of 500 c c citrated blood were given without avail. Although the number of deaths was few, it is interesting to note that three were in males. Two deaths were definitely due to reactions from the drug, and the death from toxic nephritis with uremia may well have been due to a reaction from the drug. In spite of the fact that two and possibly three out of four deaths in this series were due to the drug, we feel that the results of its use have so consistently reduced the morbidity and mortality of erysipelas in all age groups, that its merits far exceed its dangers. We wish to stress the importance of careful observation and daily blood counts on all patients while receiving the drug.

In summary

1 The literature on the treatment of erysipelas with sulfanilamide has been reviewed, showing excellent results from its use in this disease.

2 A series of 303 cases of erysipelas treated with sulfanilamide at the Los Angeles County Hospital from April 1, 1937 to August 1, 1939, is reviewed in detail.

3 The average blood level in 121 cases was 5.8 mg per 100 c c.

4 The average period of hospitalization was eight days, the average time for the temperature to reach normal was 48 hours, and the average time for the lesion to regress was 50 hours for all patients treated, and this was approximately the average for all age groups.

5 The gross mortality was 1.3 per cent for the series, which is the lowest mortality rate reported in any series to date of writing.

6 The sulfonamide drugs are the treatment of choice in erysipelas.

BIBLIOGRAPHY

- 1 MYIR-HEINL, A, and HUGUENIN, PIERRE. Treatment of erysipelas with sulphanido-chrysoidin hydrochloride, *Presse méd*, 1936, xl, 454.
- 2 KRAMER, W. Experiences with prontosil in the treatment of erysipelas, *Munchen med Wchnschr*, 1936, lxxxviii, 608.
- 3 BRFFN, G. E., and TAYLOR, I. Erysipelas treatment with prontosil, *Lancet*, 1937, i, 1334-1336.
- 4 SODGRASS, W. R., and ANDERSON, T. Prontosil in the treatment of erysipelas. A controlled series of 312 cases, *Brit Med Jr*, 1937, ii, 101-104.
- 5 SODGRASS, W. R., and ANDERSON, T. Sulfanilamide in the treatment of erysipelas, a controlled series of 270 cases, *Brit Med Jr*, 1937, ii, 1156-1159.
- 6 SODGRASS, W. R., ANDERSON, THOMAS, and RENN, J. L. Sulfanilamide in the treatment of erysipelas, *Brit Med Jr*, 1938, ii, 399-403.
- 7 TOP, F. H., and YOUNG, D. C. Sulfanilamide treatment of erysipelas, special report Herman Kiefer Hospital (September 21) 1938.
- 8 NELSON, J., RINZLER, H., and KRISIA, M. P. Sulfanilamide treatment of erysipelas, *Jr Am Med Assoc*, 1939, cxii, 1044-1045.
- 9 HOYNE, A. L., WOLF, A. A., and PRIN, L. Fatality rates in the treatment of 998 erysipelas patients, *Jr Am Med Assoc*, 1939, cxiii, 2279-2281.
- 10 STOLAN, L. E. Personal communication to L. S. S.
- 11 HOYNE, A. L. Erysipelas, *Med Rec*, 1935, cxli, 132.

SULFADIAZINE AND SODIUM SULFADIAZINE: A COMPARISON OF CERTAIN OF THEIR CLINICAL AND PHARMACOLOGIC VALUES *

By CHARLES WHEELER, M D , and NORMAN PLUMMER, M D , F A C P ,
New York, N Y

SULFADIAZINE (2-sulfanilamido-pyrimidine) and sodium sulfadiazine are following sulfathiazole and sodium sulfathiazole in experimental and clinical trial just as these thiazole derivatives followed sulfapyridine and its sodium salt. Already a number of reports ¹⁻¹⁰ on the absorption, excretion, acetylation, diffusion, toxicity, and therapeutic effects of sulfadiazine in man have appeared, but because the indication is strong that sulfadiazine and its sodium salt will displace largely the other sulfonamide drugs, additional observations on the pharmacology of this drug seem important.

Previous reports on the pharmacology of sulfadiazine have dealt primarily with the observations made following a single dose of the drug and in a few cases where it has been continued for a short period of time. The findings which we are presenting in this paper are obtained from a large series of patients treated over an extended period of time. In some instances it represents daily observations of blood and urine concentrations correlated with the clinical status of the patient for periods up to two months. Furthermore, in this study we have interested ourselves in sodium sulfadiazine and have used it orally as well as intravenously. Sodium sulfadiazine can be readily administered intravenously, giving almost immediate high blood concentrations. When given in a dosage sufficient to produce blood levels even to 50 mg per cent, no immediate or subsequent serious toxic reactions followed. After the oral administration of sodium sulfadiazine and sulfadiazine in equal dosage, a comparison of the absorption curves shows that the sodium salt is more rapidly absorbed and its concentration in the blood reaches a higher level. These findings seem to have definite practical significance.

MATERIALS AND METHODS

The patients observed in this study were all adult males and females with body weights within the usual range of 50 to 80 kg, who were patients on the pavilions of The New York Hospital †. They suffered from a variety

* Received for publication November 20, 1941.

From The New York Hospital and the Departments of Medicine and Pharmacology, Cornell University Medical College.

Directed by the Committee on Chemotherapy, Cornell University Medical College, composed of Dr William DeWitt Andrus, Dr McKeen Cattell, Dr Russell L Cecil, Dr Vincent du Vigneaud, Dr Claude E Forkner, Chairman, Dr Frank Glenn, and Dr Norman Plummer.

The drugs used in this investigation were supplied by the Lederle Laboratories, Inc.

† Some infants and children are included in the data relating to the incidence of toxic effects.

of bacterial infections. Pneumonia, acute bronchitis, chronic bronchiectasis, chronic lung abscess, and subacute bacterial endocarditis make up the majority of the included diagnoses. A few of the patients were essentially normal individuals convalescing from transient illnesses of various sorts. None of the patients included for study of the absorption and excretion curves suffered from renal insufficiency, retention of urine, oliguria, congestive heart failure, or other conditions which might disturb the usual readings.

Blood specimens for determinations of drug level were mixed with potassium oxalate to prevent clotting, and both blood and urine specimens were kept in the refrigerator until analysis was made. When blood specimens were taken daily, the blood was drawn at the same time each day (between the hours 8 and 9 a.m.). All determinations of drug in urine and other body fluids were made in the Chemotherapy Laboratory of The New York Hospital by technicians especially trained in this work.

For the measurement of urinary excretion, collection of urine was started at the same time that the first dose of drug was given, and continued after the drug was stopped until only traces were detectable in the urine. All urine specimens were collected individually as voided, and later were put together to make 24-hour specimens. The volume of each urine specimen was measured, and determinations of the concentration of both free and total drug were made on every specimen. When a precipitate of drug was present in a urine specimen, the specimen was shaken well to insure dispersion of the crystals throughout the specimen before a portion was pipetted off for analysis. When collection of a 24-hour specimen was incomplete, the data for that day were discarded.

Determinations of the amounts of drug in urine and body fluids were made by the method of Bratton and Marshall¹¹. Except where specifically stated in the text, values for sodium sulfadiazine have not been altered to allow for the difference in molecular weight between sulfadiazine and sodium sulfadiazine.*

Patients who received sulfadiazine or sodium sulfadiazine by mouth were given an initial dose of either 2.0 or 4.0 gm. and then 1.0 gm. every four hours day and night. Sulfadiazine was given in the form of 0.5 gm. tablets and sodium sulfadiazine in gelatin capsules containing 0.5 gm. of the drug. Sodium sulfadiazine for intravenous use was administered as a 5 per cent solution in distilled water, made by diluting the 10 c.c. ampoule of 25 per cent solution supplied by the manufacturer. The dose was usually 2.5 gm., and this was injected intravenously over a period of 5 to 10 minutes. Injections were repeated at varying intervals in different patients, usually between six and eight hours. No local reactions, such as sloughs or venous thromboses, and no general reactions were encountered as a consequence of giving the drug by this method.

* The molecular weight of sodium sulfadiazine is 273. The molecular weight of sulfadiazine is 250.

SULFADIAZINE AND SODIUM SULFADIAZINE

ABSORPTION INTO THE BLOOD

Comparison of Sulfadiazine and Sodium Sulfadiazine when Given Orally
 Curves, representing the average absorption into the blood following the oral administration of sulfadiazine and sodium sulfadiazine in a dosage of 2.0 gm initially, followed by 1 gm every four hours, are shown in figure 1, and the range of these values is shown in table 1. These data show that the values for free and total drug throughout the first 48 hours of treatment are appreciably higher following the use of sodium sulfadiazine. The degree of acetylation is about the same for both drugs. While the maintenance dose of 1.0 gm every four hours has been widely accepted, there has been a great difference of opinion regarding the optimum amount of the initial dose of these drugs. For this reason, we considered it essential to make studies of

AVERAGE BLOOD LEVELS AFTER SULFADIAZINE AND SODIUM SULFADIAZINE

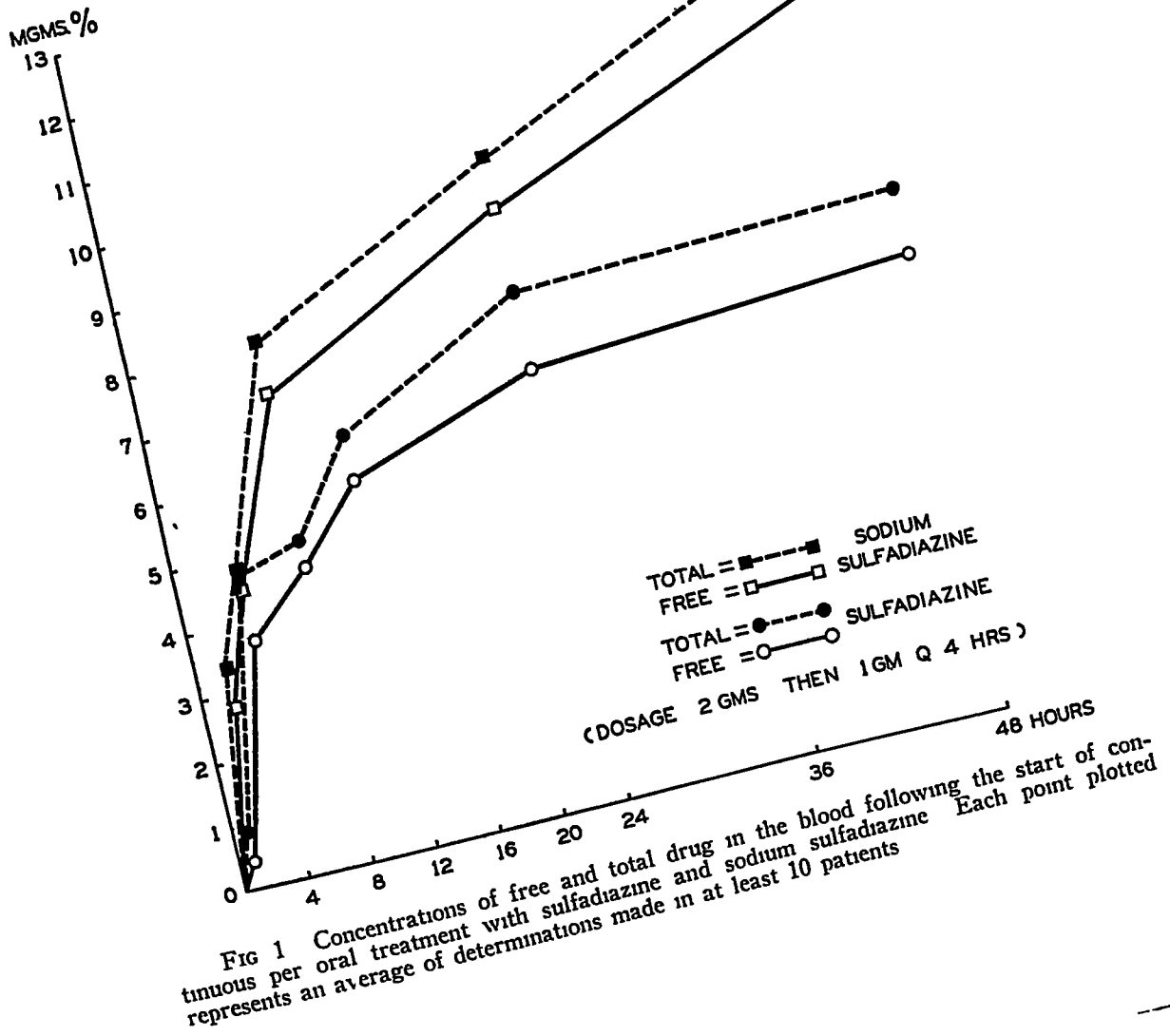


TABLE I

Blood Concentrations of Free Drug (in Milligrams Per Cent) Following Continuous Oral Dosage with Sulfadiazine (Dosage Initial Dose of 2.0 or 4.0 gm, Followed by 1.0 gm Every 4 Hours)

Hours After First Dose	Sulfadiazine						Sodium Sulfadiazine					
	Initial Dose 2.0 gm (10 patients)			Initial Dose 4.0 gm (14 patients)			Initial Dose 2.0 gm (10 patients)			Initial Dose 4.0 gm (11 patients)		
	Low	High	Average	Low	High	Average	Low	High	Average	Low	High	Average
1	0.0	1.4	0.4	—	—	—	—	—	—	—	—	—
2	—	—	—	1.2	6.4	4.0	trace	5.0	2.8	3.1	14.2	6.7
4	1.4	7.4	3.8	2.4	8.3	6.3	1.8	9.3	4.5	5.5	14.8	7.9
8	2.2	9.6	4.6	—	—	—	3.7	12.5	7.3	—	—	—
12	3.1	9.0	5.7	—	—	—	—	—	—	—	—	—
24	4.4	10.2	6.7	—	—	—	5.7	16.6	9.2	—	—	—
48	6.6	10.6	7.1	—	—	—	5.4	16.6	11.6	—	—	—

the absorption into the blood after a larger initial dose. Accordingly, determinations of the levels of free and total drug were made at two- and four-hour intervals after the oral administration of 4.0 gm of sulfadiazine and of 4.0 gm of sodium sulfadiazine. The average blood levels observed following these doses are shown in figure 2, and the range of values in table 1. Comparison of the levels in the blood following 2.0 and 4.0 gm doses of both drugs (figures 1 and 2, and table 1) reveals that the 4.0 gm dose yields considerably higher levels at the end of both two and four hours in each case. Table 1 shows that there is marked variation in individual patients with respect to the levels of drug observed in the blood following identical doses of the same drug. In this respect, no particular difference was noted between the absorption of the base or the sodium salt. Determinations after the larger initial doses again showed that the acetylation was almost the same after the administration of the two different preparations.

Observations during Prolonged Treatment The duration of treatment of the patients studied is shown in table 4. Analysis of the data regarding the blood concentrations in the 147 patients who received continuous oral dosage of sulfadiazine and the 50 who received similar dosage of sodium sulfadiazine shows that blood concentrations of free drug of between 8 and 12 mg per cent were usually obtained following the use of sulfadiazine, and of between 12 and 15 mg per cent following sodium sulfadiazine. In the instance of sulfadiazine, the proportion of drug present in the blood in the acetylated form averaged about 10 per cent of the total, while in that of sodium sulfadiazine the value was 13 per cent. It was observed also that after the first 48 hours of treatment neither the concentration of free drug nor the degree of acetylation increased. Regardless of the duration of treatment, when the drugs were withdrawn, the blood level of total drug fell to about 2.0 mg per cent within 36 to 48 hours and to a trace by the end of 72 hours. The blood level maintained in different patients receiving the

BLOOD LEVELS FOLLOWING SINGLE 4 GM. DOSES
OF
SULFADIAZINE AND SODIUM SULFADIAZINE

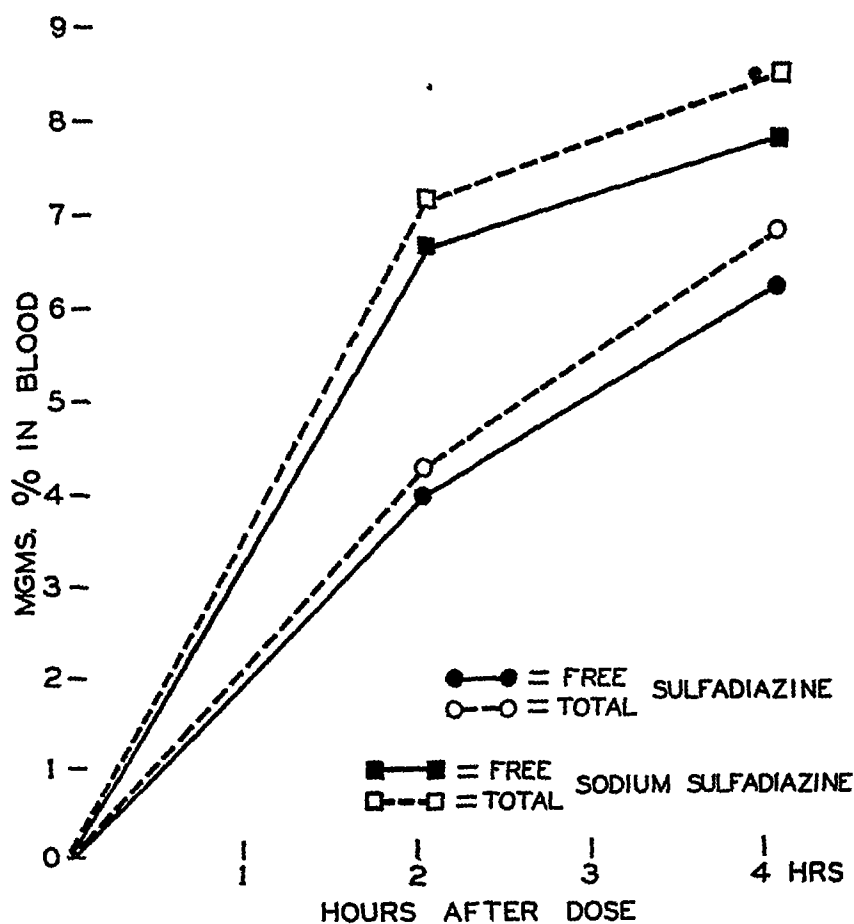


FIG 2 Concentrations of free and total drug in the blood at intervals of 2 and 4 hours after single doses of 4 gm of sulfadiazine and sodium sulfadiazine given by mouth. Each point plotted represents an average of determinations made in at least 10 patients.

same dosage of drug varied considerably. A considerable variation in the per cent conjugated was observed in the same patient at different times. An occasional patient on some days exhibited conjugation as high as 20 to 30 per cent, whereas on other days the conjugated fraction was imperceptible. No patients were encountered who consistently showed more than 15 per cent of acetylated drug in the blood following the administration of either sulfadiazine or its sodium salt.

Intravenous Use of Sodium Sulfadiazine Intravenous injections of sodium sulfadiazine were given to 21 patients, the individual dose being 2.5 gm. One patient received 13 injections, three patients 8, two patients 6, thirteen patients from 2 to 4 injections, and two patients received only a single treatment. The interval between injections was usually from 4 to 10

hours, depending upon the exigencies of the case The curves of blood levels for 24 hours following single doses of 2.5 gm of sodium sulfadiazine given intravenously are shown in figure 3 Following the administration of repeated doses by intravenous injection, in individual patients there is marked and unpredictable variation in the blood concentrations Some patients at a given time exhibited levels of 30 to 40 mg per cent of the total drug, while others who had received identical dosage of drug and in whom the levels were taken at comparable times in relation to the doses showed levels of only 10 to 15 mg per cent of total drug For example, Patient C A received

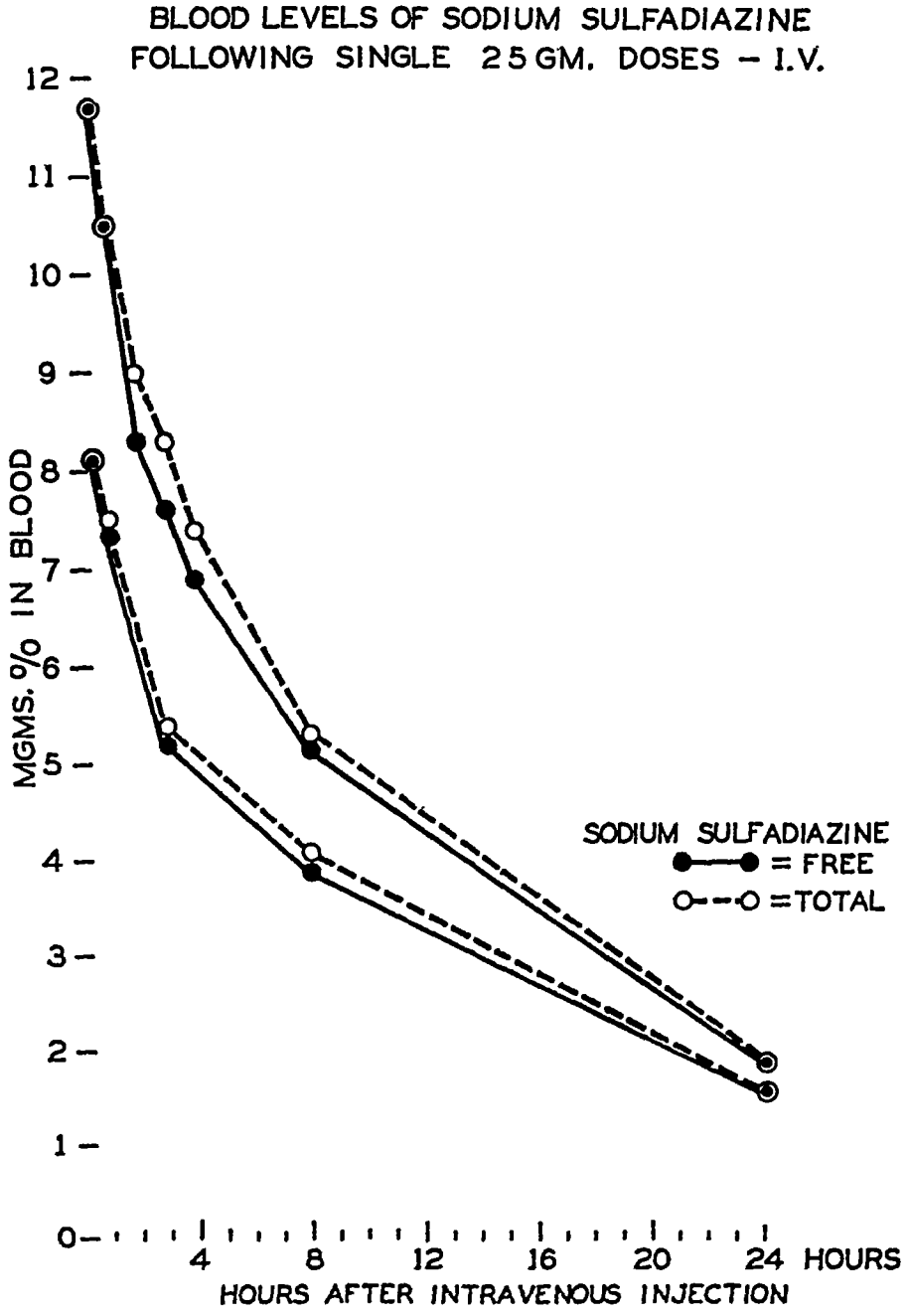


FIG. 3 Concentrations of free and total drug in the blood after an intravenous injection of 2.5 gm of sodium sulfadiazine. The values observed in 2 patients are represented

SULFADIAZINE AND SODIUM SULFADIAZINE

SULFADIAZINE: EXCRETION IN URINE
DURING COURSE OF TREATMENT

DOSAGE - 2 GM THEN 1 GM Q 4 HRS

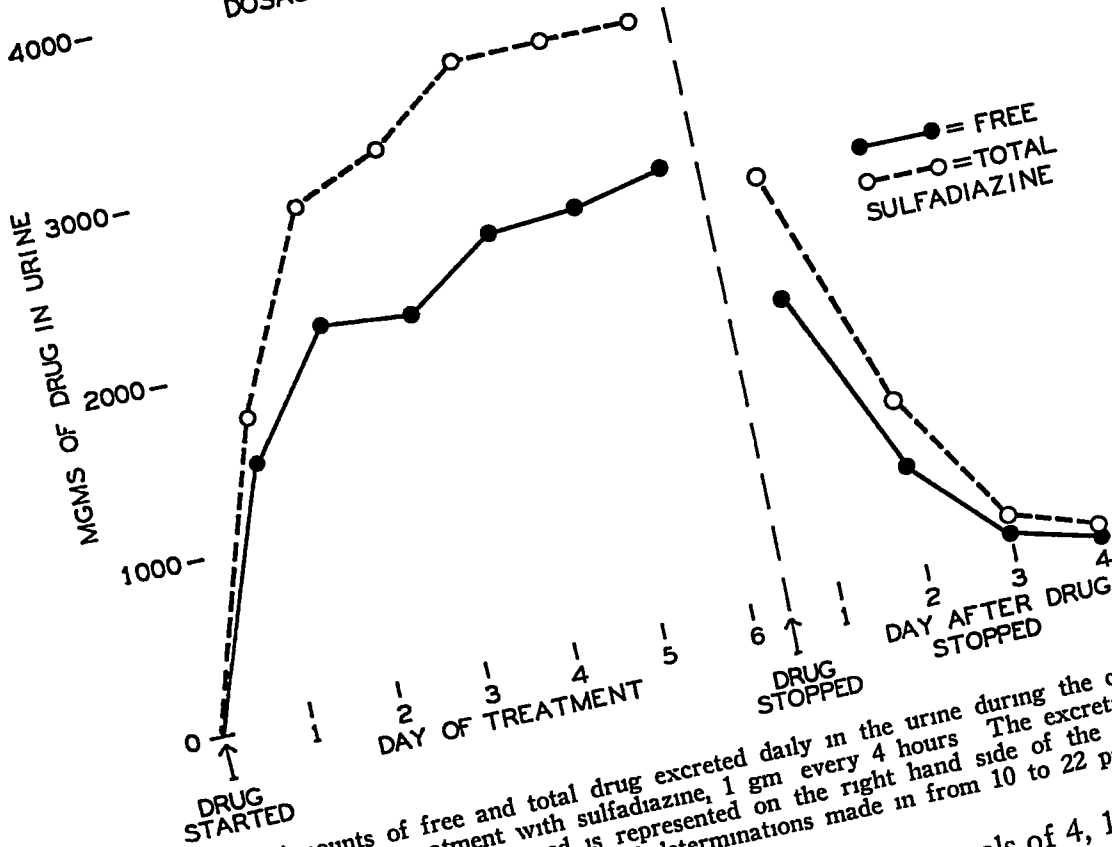


FIG 4 Amounts of free and total drug excreted daily in the urine during the course of continuous per oral treatment with sulfadiazine, 1 gm every 4 hours. The excretion of the drug after treatment was stopped is represented on the right hand side of the figure. Each point plotted represents an average of determinations made in from 10 to 22 patients.

an initial dose of 2.5 gm and three additional doses at intervals of 4, 12, and 20 hours after the initial injection, making a total of 10 gm in 20 hours. A blood level was taken 17 hours after the last injection, and this was 44.4 mg per cent of total drug. On the other hand, Patient G. A received the same dosage of drug at the same intervals of time, but in this instance a blood level taken 17 hours after the last injection was only 12.9 mg per cent of total drug. In general, we observed that two injections at an interval of 4 to 6 hours followed by subsequent injections every 8 to 12 hours provided levels rarely above 20 mg per cent just after an injection or below 10 mg per cent shortly before the next injection. When injections were continued at intervals of four to six hours, blood levels of 40 to 50 mg per cent of the free drug were observed usually after the third or fourth injection. It is important to emphasize the unpredictable way in which frequent determinations of the blood levels be made when more than a single injection of the drug is given.

The proportion of the drug present in the conjugated form following intravenous administration is usually less than that observed following oral treatment. It is generally less than 5 per cent of the total, but in rare instances is as high as 30 per cent. Again, when intravenous treatment is continued for several days, there is no tendency for the conjugated fraction to increase over that which occurs shortly after the start.

URINARY EXCRETION OF SULFADIAZINE AND SODIUM SULFADIAZINE

The urinary excretion of sulfadiazine and sodium sulfadiazine was studied throughout the course of per oral treatment in 22 patients who received an initial dose of 2 gm of sulfadiazine followed by 1 gm every four hours, and in another 22 patients who received identical dosage of sodium sulfadiazine. The average length of time during which these patients received the drugs was six days, but in a few patients it was possible to continue observations over periods as long as 28 days. The urinary excretion of the two drugs was in general the same (figures 4 and 5). The amount

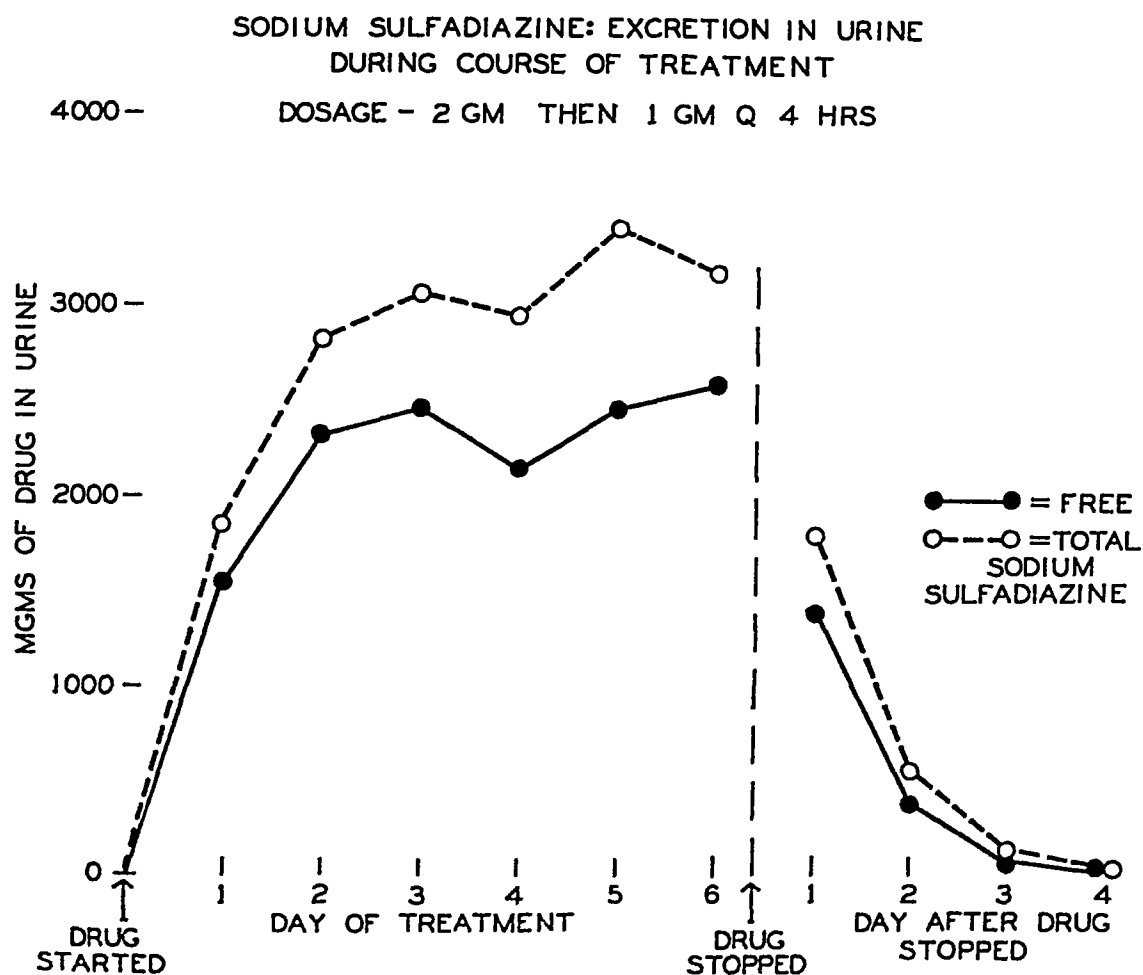


FIG 5 The same data shown in figure 4 for sulfadiazine are represented here for sodium sulfadiazine. In this figure also, each point plotted represents an average of determinations made in from 10 to 22 patients.

TABLE II
Daily Volume of Urine, Urinary Excretion, and Blood Concentration During Treatment with Sulfadiazine and Sodium Sulfadiazine

Day of Treatment	B R, male, aged 34 years Subacute Bacterial Endocarditis				L E, male, aged 45 years Subacute Bacterial Endocarditis				S T, male, aged 43 years Subacute Bacterial Endocarditis				B U, male, aged 21 years Meningococcus Meningitis				C O, female, 24 years. Lobar Pneumonia				T U, female 26 years. Pyelitis			
	Dose of Drug* (Gm)		Concentration of Drug (Mg %)		Dose of Drug* (Gm)		Concentration of Drug (Mg %)		Dose of Drug* (Gm)		Concentration of Drug (Mg %)		Dose of Drug* (Gm)		Concentration of Drug (Mg %)		Dose of Drug* (Gm)		Concentration of Drug (Mg %)		Dose of Drug* (Gm)		Concentration of Drug (Mg %)	
	Free	To-tal	Free	To-tal	Free	To-tal	Free	To-tal	Free	To-tal	Free	To-tal	Free	To-tal	Free	To-tal	Free	To-tal	Free	To-tal	Free	To-tal	Free	To-tal
1	117	117	96	112	16	16	108	111	276	348	09	81	81	167	190	04	—	—	—	—	4 S	—	—	—
2	119	119	31	41	18	18	121	125	200	308	11	100	111	200	308	11	—	—	—	—	6 S	—	—	—
3	137	137	153	170	88	17	121	125	200	308	11	121	125	200	308	11	—	—	—	—	6 S	—	—	—
4	150	150	181	174	200	05	121	125	200	308	11	111	117	108	148	24	—	—	—	—	—	—	—	—
5	148	148	160	170	325	09	133	135	372	381	07	111	117	108	148	24	—	—	—	—	—	—	—	—
6	210	210	222	180	328	05	133	135	444	460	10	125	129	114	154	20	—	—	—	—	—	—	—	—
7	290	290	385	104	338	08	—	—	457	533	06	80	90	—	—	—	—	—	—	—	—	—	—	—
8	274	274	285	200	318	18	—	—	533	615	10	70	78	—	—	—	—	—	—	—	—	—	—	—
9	210	210	222	180	328	05	—	—	502	668	09	86	92	—	—	—	—	—	—	—	—	—	—	—
10	142	142	153	205	222	17	14	162	500	571	06	71	75	222	250	10	—	—	—	—	—	—	—	—
11	137	137	140	203	230	23	—	—	410	470	07	76	76	174	250	09	—	—	—	—	—	—	—	—
12	173	173	174	210	267	07	16	200	302	372	06	76	76	286	364	12	—	—	—	—	—	—	—	—
13	173	173	173	143	182	08	—	—	271	332	06	90	93	286	400	11	—	—	—	—	—	—	—	—
14	142	142	153	205	222	17	—	—	280	533	08	71	74	250	308	11	—	—	—	—	—	—	—	—
15	142	142	147	174	242	10	—	—	142	320	421	09	70	70	167	200	18	—	—	—	—	—	—	—
16	121	121	125	190	210	11	—	—	190	200	09	75	76	200	235	18	—	—	—	—	—	—	—	—
17	148	148	150	126	133	21	—	—	—	286	364	09	80	80	160	200	20	25 iv, 6 S	—	—	—	—	—	—
18	153	153	155	118	148	13	—	—	129	134	254	267	12	75	80	190	250	20	—	—	—	—	—	—
19	121	121	125	167	170	12	—	—	266	276	12	72	78	190	250	16	6 S	—	—	—	—	—	—	—
20	153	153	158	190	190	15	—	—	—	235	320	08	70	74	211	250	11	—	—	—	—	—	—	—
21	118	118	150	228	207	13	—	—	—	262	364	05	67	71	167	200	19	—	—	—	—	—	—	—
22	129	129	135	200	216	11	—	—	—	342	533	05	70	72	133	174	20	—	—	—	—	—	—	—
23	125	125	133	200	267	12	—	—	447	166	—	71	97	190	200	20	—	—	—	—	—	—	—	—
24	388	388	129	131	151	182	24	—	—	—	—	—	67	88	121	167	28	—	—	—	—	—	—	—
25	126	126	129	170	182	08	—	—	—	—	—	—	67	88	121	167	28	—	—	—	—	—	—	—
26	112	112	153	170	182	08	—	—	—	—	—	—	59	80	—	—	—	—	—	—	—	—	—	—
27	133	133	142	157	182	12	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
28	137	137	153	170	228	13	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
29	160	160	173	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

* IV = Sodium Sulfadiazine intravenously SS = Sodium Sulfadiazine orally S = Sulfadiazine orally SP = Sulfapyridine orally

was as low as 1 gm or as high as 8 gm in a single 24-hour period, but averaged about 3.5 gm. The concentration of drug in the 24-hour urine specimen was roughly proportional to the daily volume of urine. After the third day of treatment the concentration of total drug in the 24-hour urine specimen usually remained between 200 and 300 mg per cent. There appeared to be no relationship between the total amount of drug excreted daily in the urine and the daily volume of urine unless this exceeded 2000 c c. When the daily excretion of drug in the urine exceeded 4 gm, it was usually in association with a 24-hour urine volume of more than 2000 c c, and whenever exceptionally large amounts of the drugs, such as 6 to 8 gm, were excreted in the urine in a single day, the volume of urine on that day usually exceeded 3000 c c. These data are illustrated in table 2.

When administration of the drugs was stopped, excretion of the drug remaining in the body or unabsorbed in the gastrointestinal tract was rapid (figures 4 and 5). In rare instances the excretion was prolonged for as long as eight days, even though the urinary output during this period was as good as the average for the group. The time required to excrete all of the drug after administration was stopped was essentially the same regardless of the duration of treatment.

The per cent conjugated averaged 30 per cent for the patients who received sulfadiazine and 23 per cent for those who received sodium sulfadiazine. Only an occasional patient maintained more than 50 per cent of the acetylated drug in the urine, and many never exhibited more than 15 per cent. No tendency to increase the conjugation was observed when treatment was continued as long as four weeks (table 2). An average of about 60 per cent of the total amount of drug given was recovered from the urine in the case of both drugs, the range of values being from 43 to 85 per cent*.

The urinary excretion of the drug in the 21 patients who received sodium sulfadiazine intravenously was also studied. The concentrations of total drug observed in the urine of these patients rarely exceeded 300 mg per cent even when the blood level of total drug was 30 to 40 mg per cent. It was usually between 100 and 200 mg per cent, when injections were being given at intervals of four to six hours. The proportion of drug conjugated varied from 3 to 60 per cent in the same patient at different times, but was usually between 20 to 30 per cent. In a single patient in whom collection of urine was complete, 90 per cent of the drug was recovered in the urine over a period of 48 hours following a single injection of 2.5 gm.

DIFFUSION OF SULFADIAZINE

In nine patients simultaneous determinations of the concentration of sulfadiazine in the blood and cerebrospinal fluid were made during the course of treatment. In three of these the concentration of total drug was higher

* These data are based on correction of the data relating to sodium sulfadiazine for the difference in molecular weight between sulfadiazine and sodium sulfadiazine.

TABLE III
Age Distribution of 218 Cases Treated with Sulfadiazine and Sodium Sulfadiazine

Age (Years)	Number of Cases Treated		
	Sulfadiazine Orally (1 gm q 4 hr)	Sodium Sulfadiazine	
		Orally (1 gm q 4 hr)	Intravenously (see text)
0- 1	3	0	1
1- 5	6	0	2
5-15	7	2	1
15-25	28	4	3
25-40	35	12	6
40-60	46	22	6
60-80	22	10	2
Total Cases	147	50	21

in the cerebrospinal fluid than in the blood,* and in the other six cases it varied between 49 and 100 per cent of that in the blood, averaging 72 per cent. The concentrations of total drug in the cerebrospinal fluids of these patients varied between 2 and 17.3 mg per cent, averaging 7.5 mg per cent. In three patients simultaneous determinations of the concentration of sulfa-

TABLE IV
Distribution of 218 Cases Treated with Sulfadiazine and Sodium Sulfadiazine According to Duration of Treatment

Duration of Treatment (Days)	Number of Cases Treated		
	Sulfadiazine Orally (1 gm q 4 hr)	Sodium Sulfadiazine	
		Orally (1 gm q 4 hr)	Intravenously (see text)
1- 2	2	16	
3- 7	62	21	
7-14	52	11	
14-21	18	2	
21-28	8	0	
28-35	2	0	
35-42	2	0	
63-72	1	0	
Total Cases	147	50	21

diazine in the pleural fluid and in the blood were made during the course of treatment. In these three cases, the concentrations of total drug in the pleural fluid were 74, 90, and 91 per cent of those in the blood, and the concentrations of total drug in the pleural fluid were 15.7, 4.6, and 11.7 mg per cent respectively. In a single patient simultaneous determinations of the

* Every effort was made to avoid contamination of the specimens with novocaine, but the possibility remains that such contamination did occur and that this explains the finding of higher concentrations in the cerebrospinal fluid than in the blood.

concentration of sulfadiazine in ascitic fluid and in blood were made, a concentration of total drug of 4.0 mg per cent in the ascitic fluid, and of 5.7 mg per cent in the blood being observed

INCIDENCE AND NATURE OF TOXIC REACTIONS

The distribution of the patients included in this study according to age and duration of treatment is shown in tables 3 and 4. The nature and a few

TABLE V
Toxic Reactions Occurring in 218 Cases

Case No	Age in Yrs	Sex	Diagnosis	Type of Reaction	Day of Treatment Reaction Occurred	Amount of Drug Given when Reaction Occurred Grams	Blood Level on Day Reaction Occurred mg %	
							Free	Total
Cases Treated with Sulfadiazine								
1	26	F	Lobar pneumonia	Pain in both flanks and gross hematuria	4	17	4.4	—
2	75	F	Bronchopneumonia	Pain in both flanks and gross hematuria	8	41	20.0	21.0
3	62	F	Carcinoma of esophagus, postoperative wound infection	Gross hematuria (no pain in flank)	3	11	12.5	—
4	52	M	Pulmonary tbc, acute bronchitis	Pain in left flank, gross hematuria	8	43	14.5	20.0
5	46	F	Sinusitis, bronchial asthma	Skin eruption	13	64	12.5	—
6	23	F	Acute pharyngitis (Beta hemo strep)	Skin eruption	9	38	8.8	11.1
7	21	M	Meningococcal meningitis	Skin eruption	9	51	—	—
8	23	M	Subacute bacterial endocarditis	Pyrexia of 39.6° C. Fall in WBC from 7600 to 2400	23	131	10.6	—
9	52	F	Dermatitis	Pyrexia of 39.6° C	9	20	7.2	—
10	43	M	Subacute bacterial endocarditis	Mild peripheral neuritis	16	95	7.5	7.6
Cases Treated with Sodium Sulfadiazine								
11	9	F	Scarlet fever	Pain in right flank, gross hematuria	1	8	11.7	12.5
12	50	F	Lobar pneumonia	Pain in left flank, gross hematuria	8	40	8.5	9.7
13	45	M	Subacute bacterial endocarditis	Skin eruption	9	55	13.3	13.5
14	6	F	Scarlet fever	Skin eruption	6	15	5.4	7.1
15*	43	M	Subacute bacterial endocarditis	Skin eruption	2	SD 16 SSD 5	10.1	11.1
16†	21	M	Meningococcal meningitis	Stomatitis	16	SD 96 SSD 5	7.5	8.6

* Two intravenous injections of 2.5 gm. of sodium sulfadiazine given on day before skin rash appeared, in addition to 16 gm. of sulfadiazine given by mouth before rash appeared.
† Two intravenous injections of 2.5 gm. of sodium sulfadiazine given on day before stomatitis appeared, in addition to 96 gm. of sulfadiazine which had been given by mouth.

details of the toxic reactions which we encountered in this same group following treatment with sulfadiazine and sodium sulfadiazine orally and the latter drug intravenously are presented in table 5. There was an almost complete absence of nausea and vomiting following the administration of these drugs. Only two patients, not included in table 5 and both following the use of sulfadiazine orally, exhibited this reaction. Even in those patients who exhibited blood concentrations of total drug of between 20 and 50 mg per cent, nausea and vomiting did not occur. Decrease in the amount of hemoglobin and the count of the red blood cells, cerebral effects, agranulocytosis, jaundice or other evidence of hepatitis, and cyanosis were not recognized during the course of treatment with these drugs in this series of cases.

The toxic effects did not result seriously in any instance, and subsided promptly in every case when the drugs were discontinued. The toxic effects on the kidneys perhaps should be regarded as the most serious of those encountered. In the patients who experienced colic, the pain occurred both unilaterally and bilaterally, was never severe, and did not persist for more than 12 hours. Gross hematuria was noted usually in only a single urine specimen, and in every instance subsided at the end of 24 hours. Not one patient who had experienced the toxic effect on the kidneys showed evidence of permanent renal damage. In every instance the urinalysis and renal function, as measured by ability to concentrate the urine and the urea clearance test, were normal within a few days of the time that the reaction occurred. Other patients during the course of treatment exhibited a slight or moderate increase in the number of red blood cells observable on microscopic examination of the centrifugized urine sediment. This was usually in association with considerable numbers of crystals of drug. This finding was not regarded as an indication for withdrawing the drug, and when it was continued in such cases no ill effect was observed. The skin eruptions were generalized and macular or morbilliform in character, similar to those observed with other sulfonamide drugs. There was no associated fever, and in no case did exfoliation of the skin occur. The rash subsided promptly when the drug was discontinued.

DISCUSSION

Our data indicate that continuous oral dosage of sulfadiazine results in higher blood concentrations of free drug than are usual following the same dosage of sulfapyridine^{12, 13, 14} or sulfathiazole,^{15, 16} and the values which we observed following the use of sodium sulfadiazine are even higher than those for sulfadiazine itself. These differences are illustrated in figure 6. The differences between the values observed for sulfadiazine and sodium sulfadiazine are similar to those reported for sulfapyridine^{17, 18, 19} and sulfathiazole^{17, 19} and their sodium salts.

The proportion of acetylated drug present in the blood following the oral administration of sulfadiazine and both oral and intravenous admin-

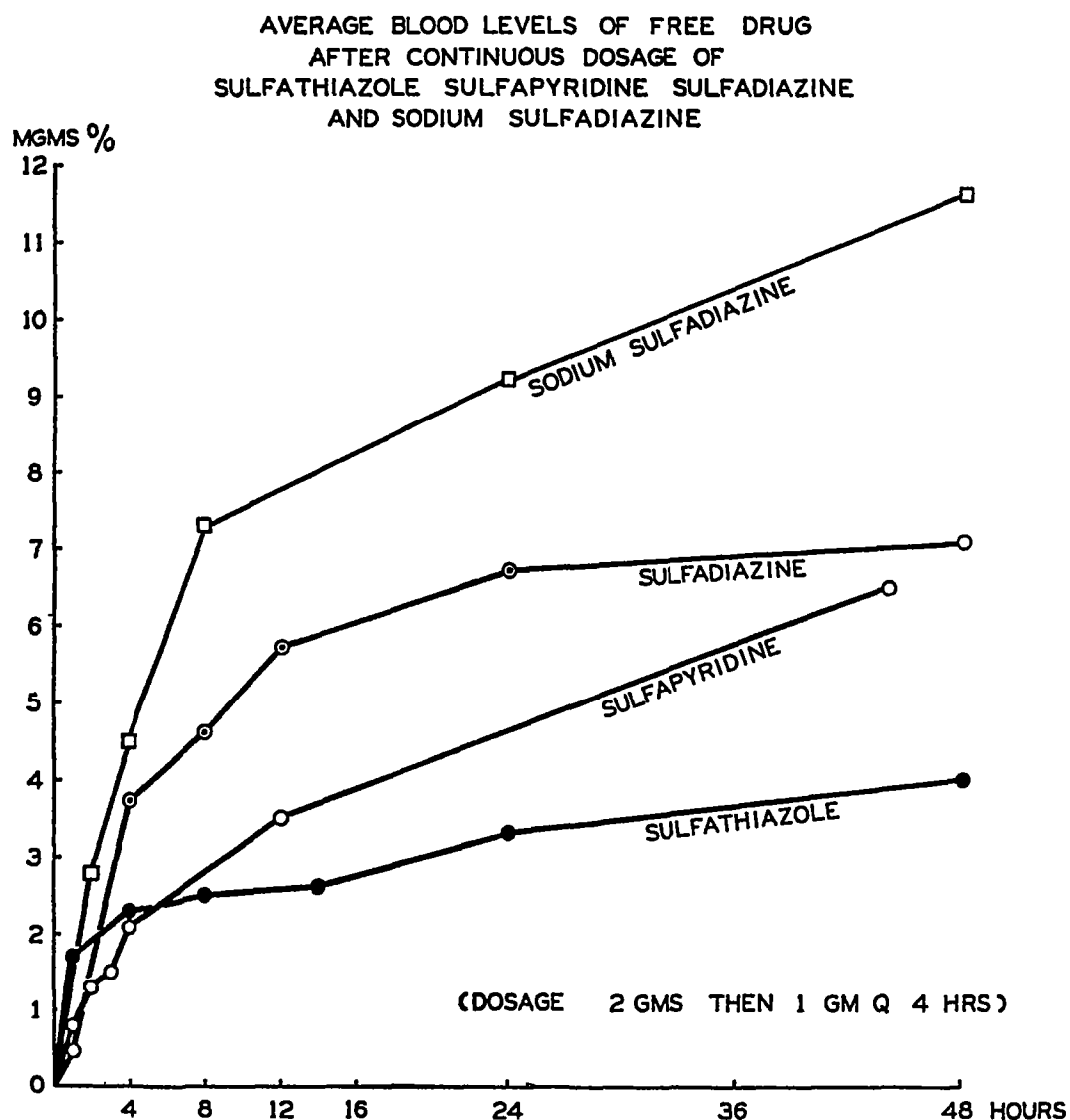


FIG 6 Concentrations of free drug in the blood after the same continuous peroral dosage of sulfapyridine, sulfathiazole, sulfadiazine, and sodium sulfadiazine. In the instances of sulfadiazine and sodium sulfadiazine, each point plotted represents the average of determinations made in at least 10 patients. The values represented for sulfapyridine are those reported by Kinsman, Moore and Harrison in the *Journal of Laboratory and Clinical Medicine* (1940, *vol.* 1235).

istration of sodium sulfadiazine was much smaller than that usually observed after sulfapyridine^{20, 21, 22} and sulfathiazole^{5, 16} and their sodium salts. Furthermore, acetylation did not increase during prolonged therapy, as has been observed in the instances of sulfanilamide²³ and sulfapyridine^{10, 22}. In this respect, sulfadiazine behaved very much like sulfathiazole¹⁰. Similarly the proportion of acetylated drug present in the urine following the use of sulfadiazine and sodium sulfadiazine was much less than that observed after the use of sulfanilamide^{21, 23, 24} or sulfapyridine,^{21, 25} and slightly less than that observed after sulfathiazole^{15, 26}. The difference between sulfadiazine and sulfapyridine in the proportion of drug excreted in the urine in the acetylated form is well shown by Patient L E in table 2. On the twentieth day of treatment sulfadiazine was discontinued and sulfapyridine given instead.

Synchronous with this change in the medication, the proportion of drug present in the acetylated form increased from less than 5 per cent to as high as 50 per cent. Again, because the relationship between the amount of drug acetylated and the production of toxic effects, sulfadiazine may possess an advantage with respect to the small percentage of acetylated drug excreted in the urine.

The data which we have available do not allow many conclusions regarding the explanation of the variations which different patients and the same patient at different times, receiving the same dose of drug, exhibit in the concentration of drug in the blood or the amount of drug excreted in the urine. There probably is a variation in the absorption of drug from the gastrointestinal tract, but the factors influencing this difference are not recognized. Similarly, there appears to be no explanation for the variations in conjugation and no definite lead to the factors influencing it. The concentration of total drug in blood or urine appeared to have no influence on acetylation. Age or sex of patient, concomitant disease, degree of pyrexia, and other similar factors appeared to have no influence on the variations described.

The data which we have presented regarding the concentration of sulfadiazine in cerebrospinal fluid and other body fluids, indicate that this drug, like sulfanilamide and sulfapyridine, and unlike sulfathiazole, is readily diffused.

There were proportionately few toxic reactions following the use of diazine derivatives. Our data do not allow many conclusions regarding the factors involved in the production of the few toxic reactions which we observed. It does not appear possible to correlate the occurrence of reactions with age, sex, diagnosis, fluid intake, urinary output, concentration of drug in the blood, or proportion of the drug acetylated. Although the blood levels observed in some patients at the time of a toxic reaction were higher than the average, in others they were lower. A number of patients who had high levels either transiently or over long periods of time never experienced any toxic effect. Only one patient (Case 2, table 5) out of a group of 15, who at one time or another exhibited a blood concentration of total drug of 15 mg per cent or higher following administration of sulfadiazine or sodium sulfadiazine, developed a toxic reaction. Our data are of particular interest relating to the occurrence of pain in the flank and gross hematuria. In two patients (Cases 4 and 12, table 5), this reaction occurred during the course of studies of the urinary excretion of drug. But in both cases the daily volume of urine, the concentration of total drug in the urine, and the proportion of acetylated drug in the blood and urine revealed no significant differences from the usual findings in our other patients. The readings were within the average range both on the day on which the reaction occurred, and on the days preceding and following. Furthermore, this renal irritation was not noted in any of the patients who exhibited unusually high values for either the concentration of total drug in the urine (as high as 600 mg per

cent) or proportion of drug acetylated in the urine (as high as 60 per cent) In a third patient (Case 11, table 5), the urine on the day following the occurrence of flank pain and hematuria, and on all subsequent days during the course of treatment, was within the average range for all determinations mentioned above, but unfortunately it was not studied on the days preceding the reaction These findings suggest that the renal toxic effects following the use of these drugs, and possibly other types of reactions, occur on some other basis than on that of unusual concentration in the blood or urine or degree of acetylation

SUMMARY AND CONCLUSIONS

1 The absorption, excretion and acetylation of sulfadiazine, given orally, and of sodium sulfadiazine, given both orally and intravenously, have been studied in 218 patients who received these drugs over long periods of time The toxic effects which occurred in these patients have been correlated with the pharmacological data available

2 Sulfadiazine given orally yields higher concentrations of drug in the blood and smaller proportions of acetylated drug in the blood and in the urine than do any of the other sulfonamide drugs in general use except sulfonamide This is a confirmation of earlier reports

3 Sodium sulfadiazine after oral administration yields even higher concentrations of drug in the blood than does sulfadiazine, and like the latter is acetylated to only a slight degree in the blood and in the urine

4 Initial doses of 4 grams of sulfadiazine and of sodium sulfadiazine were observed to be much more effective than initial doses of 2 grams in establishing high concentrations in the blood soon after the start of treatment

5 Sodium sulfadiazine given intravenously yields high levels of drug in the blood, is acetylated to only a slight degree, and appears to be relatively non-toxic

6 Toxic reactions after sulfadiazine treatment were less frequent and less serious than after the use of other sulfonamide drugs This, together with the high concentration of free drug obtainable in the blood, suggests that pharmacologically sulfadiazine and sodium sulfadiazine possess definite advantages over the other sulfonamide drugs in general use

BIBLIOGRAPHY

- 1 PLUMMER, NORMAN, and ENSWORTH, H K Absorption and excretion of sulfadiazine, *Proc Soc Exper Biol and Med*, 1940, *xlv*, 734
- 2 REINHOLD, J G, FLIPPIN, H F, SCHWARTZ, L, and DOMY, A H The absorption, distribution and excretion of 2-sulfanilamido pyrimidine (sulfapyrimidine, sulfadiazine) in man, *Am Jr Med Sci*, 1941, *cc*, 106
- 3 PETERSON, O L, STRAUSS, S, TAYLOR, F H L, and FINLAND, M Absorption, excretion and distribution of sulfadiazine (2-Sulfanilamido pyrimidine), *Am Jr Med Sci*, 1941, *cc*, 357
- 4 SANDER, J F, JR, and TRIBWANA, J B Observations on the absorption, excretion, diffusion and acetylation of sulfadiazine in man, *Yale Jr Biol and Med*, 1941, *xiii*, 539

- 5 FLIPPIN, H F, ROSL, S B, SCHWARTZ, L, and DOMM, A H Sulfadiazine and sulfathiazole in the treatment of pneumococcic pneumonia, *Am Jr Med Sci*, 1941, ccci, 585
- 6 PLUMMER, NORMAN, LIEBMAN, J, SOLOMON, S, KAMMFRER, W H, KALKSTEIN, M, and ENSWORTH, H K Chemotherapy versus combined chemotherapy and serum in the treatment of pneumonia A study of 607 alternated cases, *Jr Am Med Assoc*, 1941, cxvi, 2366
- 7 LONG, P H Sulfadiazine The 2-sulfanilamido pyrimidine analogue of sulfanilamide, *Jr Am Med Assoc*, 1941, cxvi, 2399
- 8 FINLAND, M, STRAUSS, E, and PETFRSON, O L Sulfadiazine Therapeutic evaluation and toxic effects on 446 patients, *Jr Am Med Assoc*, 1941, cxvi, 2641
- 9 DINGLE, J H, THOMAS, L, and MORTON, A R Treatment of meningococcic meningitis and meningococcemia with sulfadiazine, *Jr Am Med Assoc*, 1941, cxvi, 2666
- 10 DOWLING, H F, HARTMAN, C R, SUGAR, S J, and FELDMAN, H A Treatment of pneumococcic pneumonia with sulfadiazine, *Jr Am Med Assoc*, 1941, cxvii, 824
- 11 BRATTON, A C, and MARSHALL, E K, JR A new coupling component for sulfanilamide determination, *Jr Biol Chem*, 1939, cxviii, 537
- 12 CALLOMON, V B, and GOODPASTOR, W E Sulfathiazole in the treatment of pneumococcus pneumonia, *ANN INT MED*, 1940, iv, 1024
- 13 ABERNATHY, T J, DOWLING, H F, and HARTMAN, C R The treatment of lobar pneumonia with sulfapyridine and sodium sulfapyridine with observations upon effective blood levels, *ANN INT MED*, 1940, xiii, 1121
- 14 WINTERS, W L, RHOADS, P S, WAYNE, W F, and ROSI, R The treatment of pneumococcic pneumonia with sulfapyridine, *ANN INT MED*, 1941, xiv, 1827
- 15 REINHOLD, J G, FLIPPIN, H F, and SCHWARTZ, L Observations on the pharmacology and toxicology of sulfathiazole in man, *Am Jr Med Sci*, 1940, cxcix, 393
- 16 FLIPPIN, H F, REINHOLD, J G, and SCHWARTZ, L Sulfapyridine and sulfathiazole therapy in pneumococcic pneumonia, *Jr Am Med Assoc*, 1941, cxvi, 683
- 17 BARLOW, O W, and CLIVENKO, D R Studies on the pharmacology of sulfapyridine and sulfathiazole, *Jr Am Med Assoc*, 1941, cxvi, 282
- 18 RATISH, H D, DAVIDSON, A, and BULLOWA, J G M Absorption and excretion of sulfapyridine and sodium sulfapyridine in man, *Jr Pharm and Exper Therap*, 1940, lxi, 365
- 19 STRAUSS, E, LOWELL, F C, TAYLOR, F H L, and FINLAND, M Observations on the absorption, excretion, and distribution of sulfanilamide, sulfapyridine, sulfathiazole, and sulfamethylthiazole, *ANN INT MED*, 1941, xiv, 1360
- 20 STOKINGER, H E Absorption, acetylation, and excretion of 2-sulfanilamid pyridine (Dagenan, M & B 693), *Proc Soc Exper Biol and Med*, 1939, xl, 61
- 21 LONG, P H, and FEINSTONE, W H Observations upon the absorption and excretion of sulfapyridine (2-sulfanilyl aminopyridine), *Proc Soc Exper Biol and Med*, 1938, xxxix, 486
- 22 LONG, P H, and WOOD, W B, JR Observations upon the experimental and clinical use of sulfapyridine II The treatment of pneumococcal pneumonia with sulfapyridine, *ANN INT MED*, 1939, xiii, 487
- 23 LONG, P H, and BLISS, E A The clinical and experimental use of sulfanilamide, sulfapyridine, and allied compounds, 1939, The Macmillan Co, New York
- 24 MARSHALL, E K, JR Bacterial chemotherapy The pharmacology of sulfanilamide, *Physiol Rev*, 1939, xix, 240
- 25 BROWN, W H, THORNTON, W B, and WILSON, J S Observations on the absorption, distribution, and excretion of sulfapyridine, Dagenan, or M & B 693, *Jr Clin Invest*, 1939, xviii, 803
- 26 LONG, P H, HAVILAND, J W, and EDWARDS, L B Acute toxicity, absorption, and excretion of sulfathiazole and certain of its derivatives, *Proc Soc Exper Biol and Med*, 1940, xliii, 328

THE ADVANTAGES AND CLINICAL USES OF DESICCATED PLASMA PREPARED BY THE ADTEVAC PROCESS *

By E E MUIRHEAD, M D , and J M HILL, M D , *Dallas, Texas*

THE permanent establishment and widespread use of intravenous plasma therapy are now fully realized. It has become apparent that this type of therapy is very efficacious in the handling of many pathological states, the outstanding one of which is shock. The present war and the urgencies of national defense have increased markedly the interest in this field principally because of its tremendous possibilities in military medicine. For these reasons it is the object of this communication to relate the importance of large volume production of desiccated plasma and the experience gained from its clinical use in a routine hospital service during the 21 months of its operation.

At the present time there are differences of opinion as to the concentration of plasma most desirable for use intravenously. Various concentrations have been advocated, including dilute or half-strength plasma,¹ normal or isotonic plasma² and concentrated or hypertonic plasma³. It has been suggested that the concentration used be based on the state of hydration of the tissues⁴. It is our belief, for reasons to be given subsequently, that concentrated or hypertonic plasma offers more advantages therapeutically, than other forms of plasma commonly used.

In this respect a minor feature of desiccated plasma is the choice of concentration it offers, that is, from the most dilute form of plasma up to four or five times normal concentration. This may be readily obtained by varying the amount of water or saline used as a solvent. But, of far greater value are its technical and therapeutic advantages^{5d}. For civilian and military emergencies it offers the necessary ideal storage and transportation facilities. More important, however, are the therapeutic advantages to be mentioned later in regard to shock therapy, control of plasma protein level and adjustment of abnormal fluid balance through its concentration and increased osmotic properties.

The literature on this subject continues to expand rapidly. The various reports are of a dual nature, dealing with methods of production and results of use. The importance of plasma proteins introduced as normal or isotonic plasma in shock has been emphasized by several from experimental evidence¹. The value of concentrated proteins has been demonstrated by others^{6, 7, 8}. One report considers normal and concentrated serum of equal value in shock^{9d}. Animal experimentation has also revealed evidence supporting

* Received for publication July 19, 1941.

From the William Buchanan Blood, Plasma and Serum Center, Baylor University College of Medicine, Dallas, Texas.

plasma protein therapy in burns,⁷ wound healing,^{8, 9c} liver damage,^{9, 8c} massive exudations,¹⁰ intestinal obstruction,¹¹ starvation,¹² increased intracranial pressure,¹⁷ and edemas¹¹ To supplement this there is a growing support of its importance in corresponding clinical conditions^{15, 14b, 8c, 3c, 1c} In the various reports normal or isotonic plasma has been used more widely than hypertonic plasma This is possibly due to limited facilities in the past for desiccating routinely large volumes of plasma Hypertonic plasma is being increasingly used and there are definite indications that it possesses important inherent qualities

METHODS

The methods of dehydrating plasma without denaturation of its proteins fall into two major categories, those drying from the frozen state and those drying from the liquid state The former group utilizes high vacuums under which conditions immense volumes of water vapor are given off This water vapor must be removed for dehydration to continue and here lie the basic differences between the various apparatuses used At the present time there are four major principles used in removing this water vapor, namely chemical absorption,¹⁶ cold surface condensation of water vapor,^{17, 16b} physical adsorption^{3b} and large sized vacuum pump with means to continuously separate water out of the oil¹⁸ The methods for liquid state drying are numerous¹⁹ and so far have failed to reveal the ability to handle effectively mass production quantities

Ninety-two per cent of the plasma used in the present series was first desiccated by the adtevac process^{3b} The remaining 80 per cent consists of unprocessed normal plasma given intravenously The methods of handling the plasma have been previously described^{3b, d} and only the major steps will be mentioned Blood is collected into vacuum type bottles Plasma is obtained either from blood collected expressly for this purpose or from outdated bank blood The plasma is separated from cells by means of two De Laval separators arranged in series The entire volume of blood separated each time, 25 to 50 liters, is pooled together to remove the agglutinins By this method true plasma yields of 50 per cent can be repeatedly obtained in relatively a few minutes' time Double centrifugation makes for a clear product with most of the fat content removed At this point plasma is either frozen and used later or filtered and used at once Filtration is performed by means of a Seitz bacterial filter An important feature of this step is the use of Filter cel* This substance, which has been used by commercial veterinarian biological concerns for years, makes for an improved product It encourages filtration and prevents plugging of the filter pad, it removes a great deal of the fibrinogen thus decreasing future fibrin precipitation and it helps to remove lipid particles Since we have successfully filtered plasma obtained from 1,190,000 c c of blood, we totally disagree with

* A product of Johns-Manville Sales Corporation, New York, N Y

Strumia²⁰ on this point. From the filter receptacle plasma is immediately placed in large glass ampoules, attached to the adtevac machine and dried from the frozen state. After 24 to 36 hours it is granulated and dispensed into vaccine type bottles by means of a hopper. This final step reduces the size of the container considerably thus making the dispensing package of practical size. A vacuum is drawn in the bottles so as to encourage the entrance of pyrogen free water which is used as the solvent. Each stage of this partially opened method is checked by bacterial cultures. The use of an air conditioned, dust-free room is an added safeguard.

Desiccated plasma produced in this manner is a porous, friable powder of light amber color occasionally having a pink cast. Even with the passage through the hopper the moisture content (Flosdorf-Webster method)²⁰ remains 1.0 to 2.0 per cent, thus providing for flash solubility. The product can be made to dissolve with ease in 1.5 to 2.0 minutes' time. The hemoglobin content is inconsequential, varying from 80 to 300 mg per cent in the four times concentrate²¹. The fibrinogen content is so low as to be almost negligible and the pH is elevated to about 8.4^{16b}.

In the routine service we have dispensed three different quantities of desiccated plasma containing 6.25 gm, 12.5 gm and 25 gm of the dry product. These provide for 25 c.c., 50 c.c., and 100 c.c. of hypertonic (four times concentrated) plasma respectively. Approximately 10 per cent of the final volume is deleted in estimating the amount of water added in order to allow for the solids. Thus for 100 c.c. of four times concentrated plasma 90 c.c. of water are added to 25 gm of solids. It must be mentioned that four times concentrated here is concerned with citrated plasma and not unmodified plasma. Thus the protein content averages 20 gm per cent.

We have experienced no difficulty in handling this product in syringes as mentioned by others²¹. When rushed for time the product can be dissolved and given to a patient in shock in less than three minutes.

INDICATIONS AND CONTRAINDICATIONS

The variety of cases seen in a routine service serves as a good means of testing the indications and encountering the contraindications.

Indications for Intravenous use of Hypertonic (4 × Concentrated) Plasma

- I SHOCK—rapid building of blood volume and acceleration of circulation
Excellent response in all forms of shock

- A Traumatic
- B Post-hemorrhagic
- C Shock of burns
- D Neurogenic
- E Incompatible blood transfusion

II CONTROL OF PLASMA PROTEIN LEVEL—rapid filling of protein stores, elevation, and sustainment of plasma protein level

A Hypoproteinemc states

- 1 Protein depletion after gastrointestinal operation, fistulae, starvation
- 2 Liver damage
- 3 Massive exudation—pneumonia, exudates in serous cavities, late phase of burns, large ulcerations
- 4 Protein loss—through kidney (nephrosis), gastrointestinal tract (ulcerative colitis)

B Intravenous protein feeding when food by mouth restricted

III CONTROL OF FLUID BALANCE—prolonged and powerful osmotic effects in edemas

A Edema

- 1 General severe hypoproteinemc states and after excessive intravenous saline
- 2 Local
 - a Pulmonary (preliminary bleeding to prevent increased blood volume must be done)
 - b Cerebral—head injury, brain surgery, eclampsia

B Excessive fluid and protein loss—infectious diarrhea, cholera, dysentery (together with other fluids in combating hypovolemia and hemoconcentration)

IV TO PROVIDE ANTIBODIES IN INFECTIOUS DISEASE

A Directly—convalescent plasma

B Indirectly—to maintain body protein stores at levels necessary for effective antibody formation

The outline of indications for the clinical use of concentrated plasma is self-explanatory. The evidences supporting the use of hypertonic plasma in shock, regardless of its cause, are given below. In burns, the enormous quantities of protein lost may be rapidly replenished gram for gram by this means. In moderate or profound hypoproteinemc states the protein stores and plasma protein level may be successfully restored by means of repeated large doses. Here fluid administration is frequently not essential and the concentrated product affords the best means of giving large doses intravenously. In patients who are unable to take food by mouth, as following gastrointestinal operations, a normal nitrogen balance can be maintained^{22, 12}. The giving of glucose and vitamins alone makes for an unbalanced metabolism. In edemas the increased osmotic forces help in shifting fluids from ab-

normal locations. In severe cases of pulmonary edema which are refractory to bleeding alone, the addition of concentrated plasma is of value. Here one must insure against overloading the heart by adequate preliminary bleeding. Even in severe dehydration its judicious use following other fluids may be of help. Here it acts in a manner comparable with glucose²³ by pulling in fluids given subcutaneously and encouraging an adequate renal plasma flow. Convalescent serum or plasma administered by this means may be given in greater doses, more rapidly and with less discomfort to the patient than by any other method.

There are very few contraindications to the use of concentrated plasma and this form of plasma properly prepared is innocuous. The major contraindication is the presence of incapacitating myocardial damage. In congestive heart failure the additional and sudden increase in blood volume may be dangerous. Hypertension by itself, however, is not a contraindication. Patients with a blood pressure of 200 systolic and 110 to 120 diastolic have been given substantial doses (100 to 150 c c) of four times concentrated plasma on many occasions without harmful results. Dehydration approaching the critical level of 10 per cent of the body weight²⁴ is obviously a contraindication. Even here concentrated plasma may be used in mobilizing fluids if the latter are given subcutaneously.

CLINICAL DATA

The present report relates further clinical experience with desiccated plasma, summarizing the clinical results from the inception of the routine service at Baylor University Hospital to the present time. Of necessity it overlaps with previous reports^{3a, b, c, d}.

Almost 1,000,000 c c of blood have been converted into plasma and desiccated by the adtevac process. Seventy-three thousand two hundred and thirty-seven c c (73,237 c c) have been given clinically under controlled conditions, 50,107 c c to patients in Baylor Hospital and 23,130 c c to

TABLL I

	No. Cases	Smallest Total Dose 4 X Conc Plasma c c	Largest Total Dose 4 X Conc Plasma c c
Shock Prevention	34	50	250
Burns	9	100	1200
Protein Feeding	31	50	7690
Edemas	7	50	620
Head Injuries and Neuro- surgery	32	50	300
Toxemia of Pregnancy	28	50	370
Miscellaneous	48	20	150
Total	180*	Av 53	Av 151

* Six cases included in two groups

Note: Total dose includes one to several injections

patients on the outside. The former figure is related to 276 cases that have received a total of 674 doses of four times concentrated plasma. There have been only five febrile reactions, all of pyrogenic type, making a reaction rate of 0.74 per cent.

The cases have been separated into groups in order to emphasize the importance of the introduction of large amounts of protein intravenously. The major groups, besides the shock group, are listed in table 1.

SHOCK

It is accepted that the shock syndrome results from a disparity between the circulating blood volume and the vascular capacity, due mainly to an actual decrease in blood volume.²⁵ Sooner or later the associated anoxemia, with its increased capillary permeability and seepage of plasma into the tissue spaces tends to progressively accentuate this disparity. The main purpose of shock therapy is to restore the effective or circulating blood volume as rapidly as possible, thus breaking the anoxic cycle. The disagreements regarding the pathogenesis of shock²⁶ do not invalidate this aim.

The depleted blood volume may be due to a loss of red blood cells and plasma (whole blood) or to a loss of plasma alone. In most instances the red blood cell loss, even if great, is relatively insignificant and only in rare cases does it influence the subsequent course.^{27, 5b, d, e, 4, 2d, e} In Amberson's experiments^{27b} animals appeared normal when their blood was replaced by a 12 to 14 per cent solution of free hemoglobin. Death by asphyxia occurred only when the hemoglobin content was reduced to a 3 per cent concentration.

Various solutions have been used to replenish the depleted blood volume. The evanescent and frequently ineffective results obtained with intravenous saline and glucose solutions whether in isotonic or hypertonic form, have been aptly stressed.^{28, 28a, e, b, 5a, b, e, f, g, 4, 21} These solutions may hydrate tissues to the point of producing edema but most often they fail to maintain the blood volume. Furthermore, plasma proteins may be washed out of the blood stream by their use in cases with capillary damage.^{5f} Other solutions as 6 per cent gum acacia, Ringer hemoglobin and gelatine-saline solutions have proved unsatisfactory. Although whole blood transfusions, within certain limits, are effective, the relative insignificance of the added red cells plus technical difficulties makes this procedure lose a great deal of its former value. Only in rare cases of extremely severe red cell depletion, losses approaching three-fourths to four-fifths of the circulating hemoglobin content,^{27a} are blood transfusions absolutely essential. On the other hand, the importance of plasma proteins in maintaining blood volume and combating shock meets general agreement. Therefore, in shock therapy the basic problem is one of deciding which type of protein containing fluid is most effective.

There is evidence that dilute or half-strength plasma suffers from deficiencies comparable to those of saline and glucose solutions, for the crystal-

loid containing portions of these solutions are lost to the tissues ²¹ The possible effectiveness of this procedure is not denied but it does not constitute the ideal treatment. It perhaps has its greatest value in most severe grades of dehydration.

The ideal treatment, consequently, rests between normal (isotonic) and concentrated (hypertonic) plasma. The researches of several have emphasized the value of normal plasma infusions ^{2a, b, c, d, e}. That this is an effective means of combating shock is well agreed. But, is it the most effective treatment?

Blalock and associates have shown that with widespread capillary damage large amounts of plasma and its proteins may be lost from the blood stream. This loss may continue at a rapid rate in spite of continuous intravenous administrations of plasma. It is also stressed that colloid should be given "fast enough to increase the level in the blood to the point of retaining an effective circulating volume in spite of the losses that may occur" ^{15d}. There are obvious clinical implications of these deductions. Normal or isotonic plasma may completely control shock or it may maintain circulating blood volume by enormous and multiple infusions sufficient to combat severe grades of shock. However, it serves mainly as a substitution and it does not tend to reverse the abnormal physiologic mechanisms of shock. Its normal isotonic osmotic properties make it as subject to seepage through the capillaries as the patient's own plasma. On the other hand, concentrated plasma actually tends to reverse the known mechanism of shock. It increases blood volume rapidly by withdrawing fluid from the tissues and its hypertonicity affords stimulating effects on the capillaries ^{20, 28c}. This is illustrated clinically by the rapid changes in the patient. The blood pressure response in a large majority of the patients is sudden, the pulse becomes more regular and there is obvious clinical improvement. Given rapidly and in sufficient quantities its action is quicker than that of other agents. In addition any degree of protein depletion through damaged capillaries, however great, can be coped with by rapid administration of large doses of protein. This appears to approach an ideal shock treatment.

In connection with the use of hypertonic solutions harmful dehydration is frequently discussed. Most cases of hematogenic shock, particularly in a general hospital, are sufficiently hydrated to be capable of easily supplying interstitial water to dilute 100 to 500 c c of four times concentrated plasma. Such fluid can be rapidly and effectively substituted by hypodermoclysis. By this means the risks of intravenous saline are averted. For military emergencies the subcutaneous saline is less apt to cause pyrogenic reactions thus facilitating its preparation. In this same regard the approximately 3 per cent sodium chloride concentration of the plasma is of value. The hypertonic effect of this fraction is soon lost, but it serves to hold water that is given orally or parenterally in the body, and at the same time, it discourages potassium imbalance."

ADVANTAGES AND USES OF DESICCATED PLASMA

TABLE II

Degree of Shock	No of Cases	Aver Dose cc	Results		
			Excellent	Good	Poor
Severe	45	183	26	3	5
Moderate	35	129	30	5	
Mild	13	82	12	1	
Total	93	131 3	68	9	5

CONTINUATION OF TABLE II

Degree of Shock	No of Cases	Time Interval Before Blood Pressure Above Critical Level							
		5-15 Min				15-45 Min		45-60 Min	
		No	%	No	%	No	%	No	%
Severe	45	18	40	10	22 2	6	13 3	6	13 3
Moderate	35	23	65 7	7	20	2	15 4	5	14
Mild	13	9	69 2	2	15 4	8	8 6	11	11 8
Total	93	50	53 76	19	20 43				

EXPLANATION OF TERMS IN TABLE II

- I Degree of Shock arbitrary clinical evaluation as follows
 - A Grade of Shock
 - 1 Severe signs of peripheral circulatory failure plus imperceptible or near imperceptible pulse or blood pressure, or coma
 - 2 Moderate blood pressure below critical level (80/40) and between 50 to 75 systolic and 0 to 50 diastolic and signs of peripheral circulatory failure
 - 3 Mild Blood pressure near critical level and signs of peripheral circulatory failure
 - B Grade of Response
 - 1 Excellent Sudden response of blood pressure, above critical level and gradual drop to minutes, with clinical improvement
 - 2 Good Slower blood pressure response, 45 minutes to 1 5 hours to reach 80/40 or above
 - 3 Transient Elevation of blood pressure above critical level and gradual drop to death
 - 4 Poor Blood pressure not elevated to critical level, death

Table 2 summarizes the shock cases. This classification on a clinical basis, although not ideal, is the only means of appraisal at the present time. The rapidity of action of concentrated plasma is well emphasized.

Ninety-three cases of shock have been studied thus far. All have had clinical signs of peripheral circulatory failure, that is, weak pulse with tachycardia, cold and pale skin, sweating, restlessness, mental confusion or coma, plus a depression of blood pressure. In 77 of the cases (82 8 per cent) the blood pressure was below the critical level taken as 80 mm Hg systolic and 40 mm diastolic. There were 45 cases (48 4 per cent) who received no other intravenous fluids until shock was well controlled and the blood pressure was well above the critical level, 48 cases (51 6 per cent) had both four times concentrated plasma and other intravenous fluids spaced at

shorter intervals. In all cases that responded, the response was directly related to the administration of the concentrated plasma. Only five cases or 5.36 per cent failed to respond.

In 66 cases (70.9 per cent) hemorrhage played a part in the blood volume depletion. Fifty-four cases (58 per cent) had surgical operations before treatment.

DOSES

The dose in shock depends strictly on the response. One hundred c.c. of four times concentrated plasma may be given as the initial dose to be followed by as frequent similar doses as are needed to control shock. One hundred c.c. may be given intravenously as rapidly as possible through a 19 gauge needle, taking usually one to two minutes' time. The doses have been given at this speed on numerous occasions. On one occasion it was necessary to administer 600 c.c. of four times concentrated plasma over a period of a few hours to control shock. Often 100 to 200 c.c. are sufficient.

SHOCK PREVENTION

This group consists of 34 cases in whom it was considered shock might develop. These doses were administered following accidents, preoperatively and postoperatively. Shock did not develop in any case in this group but it becomes difficult to link this directly to the administration of hypertonic plasma in each case. The prevention of shock is a promising field.

BURNS

Concerning burn cases, particularly severer grades, many have emphasized the need for maintaining the circulating plasma protein^{31, 15a, c, 1c} level. In this regard maximum therapeutic efficiency during the period of protein loss can be attained by a combination of normal and hypertonic plasma therapy. In a case with almost total body surface burn following an oil explosion, hemoconcentration was more effectively controlled when concentrated plasma was given along with normal plasma. This case passed the shock period successfully to die three weeks later of pneumonia. Another case with three-fifths body surface burn also passed the shock period successfully but died suddenly one week later. During the first four days this patient received 6,580 c.c. of normal plasma, 1,100 c.c. of four times concentrated and 100 c.c. of three times concentrated plasma plus 2,500 c.c. of 5 per cent glucose and saline given very slowly to keep the vein open. Hemoconcentration and the plasma protein level were completely controlled only by this means. On the fifth day a blood volume estimation with Evan's blue dye revealed a normal plasma volume (4,610 c.c.) with an absolute plasma protein content of 274 gm. The estimated weight of this patient was 90 kilograms.

In the burn group one case received normal plasma alone. In this instance 3,000 c.c. during the first 36 hours were sufficient to combat shock.

ADVANTAGES AND USES OF DESICCATED PLASMA

The other cases received hypertonic plasma along with normal plasma. It was felt that the absolute plasma protein content as well as the protein concentration could be more effectively maintained, particularly in burns involving over one-third the body surface, by this combination therapy.

PROTEIN FEEDING

Surgical patients for the most part receive adequate carbohydrates, crystalloids and vitamins but frequently the protein metabolism is neglected. This is particularly true of patients who have been on a semi-starvation diet due to their illness, and following gastrointestinal operations.

It has been well demonstrated that plasma proteins are utilized by body tissues.¹² Recently a case of congenital megacolon and jejunal fistula was kept in nitrogen balance by this means. This patient received 7,690 c c of four times concentrated plasma for this purpose in a total of 100 doses plus 5,000 c c of normal plasma during 43 days. If one wishes to administer 100 gm of protein intravenously to a patient in 24 hours, 50 c c of four times concentrated plasma could easily be given at intervals throughout the day. This could be accomplished in a total time of 20 minutes whereas a comparable amount of normal plasma (2,000 c c citrated plasma) would necessitate one to three hours at the least.

In the 31 cases given concentrated plasma for this purpose benefit was noticed in several. The others received small quantities making evaluation difficult.

EDEMAS

Nutritional edema, saline edema, nephrotic edema and cerebral edema are all benefited. Two cases with nephrotic syndrome gave disappointing results in spite of large doses. One was a chronic case, the other had glomerular damage. Failure of response in similar cases has been reported.^{15g, h}

HEAD INJURIES AND NEUROSURGICAL OPERATIONS

That concentrated plasma is capable of reducing increased intracranial pressure was first demonstrated in 1938.³⁰ The effect is greater and more prolonged than that of concentrated glucose. Harmful dehydration as discussed³² has not been observed.

Most of the cases in this group were surgical. The effects on intracranial pressure were not observed by manometric studies making evaluation difficult. There were no harmful results and several cases were benefited.

TOXEMIAS OF PREGNANCY

The study of 28 cases, including 12 cases of eclampsia and 16 of pre-eclampsia, has failed to show the good results expected from preliminary observations. Transient benefit was noted in several cases but a sustained control of blood pressure level was not accomplished. The diastolic level

of blood pressure is less affected. In the few favorable results mixed treatment obscured the results.

REACTIONS

Properly prepared desiccated plasma is innocuous as shown by the febrile reaction rate of 0.74 per cent, five reactions in 674 doses. Urticarial reactions are rare. Other minor discomforts include slight dull ache along the vein which can be controlled by slower administration and transient backache in parturient women seldom lasting more than five minutes. Shock patients with a full stomach have been observed to vomit once shortly after the injection. These are usually comatose patients. Two transient tetanic carpopedal spasms in children have been previously mentioned.¹⁰

COMMENT

It can now be stated that desiccated plasma can be produced safely by bulk desiccation. Furthermore, a partially open method, which is absolutely necessary for mass production, carried out in properly air-conditioned rooms by aseptic conscientious workers has been proved to be safe by extensive experience. The original objections^{17a} to this process have been overcome as proved by bacteriological and moisture content studies and the giving of 75,000 c.c. of hypertonic (four times concentrated) plasma clinically. The febrile reaction rate of 0.74 per cent speaks for itself.

At the present time others³³ have certain objections to the product in its present form in spite of the very favorable clinical trial. The proper consideration of pyrogens³⁴ is absolutely essential in appraising any reaction rate. The relatively few milligrams of hemoglobin in this plasma have no bearing on reactions, as proved by others³⁵. We have given, on occasions, large amounts of hemoglobin in the plasma without harmful results. Bacteriological checks of all phases of this method have given negative cultures repeatedly. Contamination reactions²⁰ have not been observed. The potassium content is not harmfully increased. The low moisture content encourages rapid solution.

In this communication we have purposely disregarded distinctions between plasma and serum as a therapeutic agent. The proper preparation of either gives an innocuous product. Adtevac plasma, prepared as outlined, is literally neither plasma nor serum. The use of Filter cel during Seitz filtration removes most of the fibrinogen fraction leaving a plasma that approaches serum in composition. It has been suggested that this material be called a partially defibrinated plasma.¹¹ Such a product does not produce reactions.

Hypertonic plasma offers two therapeutic weapons, first, a direct means of substantially increasing intracapillary osmotic forces, and second, a simple and effective manner of introducing large amounts of protein intravenously. These two points are of great importance in any pathological state associated with an appreciable decrease in absolute or circulating plasma protein content. This is true regardless of the cause of the protein depletion, whether

due to an inadequate intake of protein foods, decreased production of proteins, depletion of protein stores or due to loss through large capillary beds, kidneys, or wide ulcerative surfaces. With concentrated plasma any degree of clinical plasma protein loss can be coped with.

In shock these two features are of prime importance. The rapid increase in blood volume has been previously demonstrated³⁰ by the immediate and sustained dilution of hemoglobin, a drop in venous whole blood specific gravity and a lowering of the hematocrit reading. At the same time the plasma specific gravity remains about the same, meaning that the concentration of protein remains unchanged and may be increased. There are possible stimulating effects on small sized vessels and capillaries. The withdrawal of misplaced fluids places capillary and tissue function on a more normal basis. These features tend to reverse the abnormal physiologic mechanism of shock and account for the rapid clinical responses.

Following copious hemorrhages and prior to the establishment of widespread capillary damage, it has been illustrated^{37, 38b} that the lowered capillary hydrostatic pressure encourages an influx of interstitial fluid as a means of supporting the diminished blood volume. The success of this mechanism may prevent the development of post-hemorrhagic shock. If this mechanism fails, capillary damage occurs and the diminished blood volume is accentuated by seepage of plasma through the capillary walls. To be effective, intravenous saline solutions must be given before capillary damage develops or else unnecessary risks are taken. In this interval hypertonic plasma enhances an established physiologic mechanism and may prevent the development of post-hemorrhagic shock. In this regard the unfavorable observations of Black and Smith³⁸ are not supported by others. If capillary damage ensues then hypertonic plasma continues to be effective as in other types of shock.

Gamble³⁹ has pointed out that the large volume of interstitial fluid (15 per cent of body weight) provides a strong and prolonged defense for the blood plasma volume. In rigid dehydration experiments a period of 10 days with continuous withdrawal of sodium and depletion of the interstitial fluid was necessary to produce severe harmful effects. During this period the plasma volume was maintained at the expense of the interstitial fluid. By giving these findings a clinical meaning one can discern that the transient withdrawal in shock of a comparatively small volume of interstitial fluid cannot be deleterious. Of greater value is the fact that the more important of the two components of extracellular body fluid (plasma) is being sustained through a critical period. The kidneys being in a depressed state of activity this fluid is not readily lost from the body and it can be rapidly replenished later.

Recent objections²⁰ to the use of hypertonic plasma in shock lack support. It is known that the blood volume is rapidly increased following the giving of this substance^{40, 30}. Certain British workers³¹ have observed that 80 per cent of the blood pressure elevation occurs in the few minutes follow-

ing the administration of concentrated plasma. It has never been denied that normal plasma is effective in shock treatment, but we believe that it does not appear to be the most effective therapy available at the present time.

The main emphasis in this report has been on restoring the circulating blood volume because this is the most important feature of shock therapy. Other procedures, such as prevention of exposure, warm surroundings, the giving of oxygen, etc., are of additional value.

In military medicine one of the greatest problems is shock. In this regard, the need for a therapeutic agent of high efficiency coupled with ideal storage properties is essential. In shock such an agent appears to be available in properly desiccated plasma. Drying machines that are capable of successfully supporting a routine service in a 400 bed hospital are capable of expansion to meet any demands. For mass production, bulk desiccation, first mentioned by Elser,^{16b} is safe and can be easily performed^{3a, b, c, d}

CONCLUSIONS

1 Bulk separation and desiccation of plasma or serum with proper precautions is a safe procedure.

2 Bulk desiccation is essential for mass production of desiccated plasma.

3 Desiccated plasma prepared by the adtevac process as outlined is innocuous.

4 Hypertonic plasma (four times concentrated) is highly effective in combating hematogenic shock and seems to reverse the abnormal physiologic mechanism of shock.

5 Harmful dehydration of hypertonic plasma during a short interval of time appears to have been over emphasized.

6 With hypertonic plasma any degree of clinical plasma protein loss can be controlled.

7 Hypertonic plasma is the most efficient agent available at the present time for increasing intracapillary osmotic forces.

REFERENCES

- 1 (a) ELLIOTT, JOHN, TATUM, W L, and NESSFT, N. The use of plasma as a substitute for whole blood, *North Carolina Med Jr*, 1940, 1, 283.
- (b) ELLIOTT, JOHN, BLUM, G F, and TATUM, W L. Some factors and observations on the preparation and preservation of dilute plasma, *Jr Am Med Assoc*, 1940, cxv, 1006.
- (c) BLACK, D A K. The treatment of burn shock with plasma and serum, *Brit Med Jr*, 1940, ii, 693.
- 2 (a) STELLMA, MAX M, WAGNER, J A, and MONAGHAN, J F. The intravenous use of serum and plasma, fresh and preserved, *Ann Surg*, 1940, iii, 623.
- (b) STELLMA, MAX M, WAGNER, J A, and MONAGHAN, J F. The use of citrated plasma in the treatment of secondary shock, *Jr Am Med Assoc*, 1940, cxiv, 1337.
- (c) STELLMA, MAX M, and MCGRAW, JOHN J. Frozen and dried plasma for civil and military use, *Jr Am Med Assoc*, 1941, cxvi, 2378.
- (d) LEVINSKY, S O, RUBOWITZ, F E, and NECHETS, H. Human serum transfusions, *Jr Am Med Assoc*, 1940, cxv, 1163.

- (e) BRENNAN, H J Plasma transfusions in the treatment of hemorrhage, *Brit Med Jr*, 1940, i, 1047
 - (f) SCUDDER, J Studies in blood preservation, the stability of plasma proteins, *Ann Surg*, 1940, cxii, 502
 - (g) LEHMAN, E P A simple method of plasma transfusion, *Jr Am Med Assoc*, 1939, cxii, 1406
 - (h) CLEGG, J W, and DIBLE, J H The preparation and use of human serum for blood transfusion in shock, *Lancet*, 1940, ii, 294
 - (i) HILL, D K, McMICHAEL, J, and SHARPER-SCHAFER, E P Effects of serum and saline infusions, quantitative studies in man, *Lancet*, 1940, ii, 774
 - (j) HARPER, S B, OSTERBERG, A E, PRIESTLY, J T, and SELDON, T H Changes in serum protein and hemoconcentration in man, *Jr Am Med Assoc*, 1941, cxvi, 1760
- 3 (a) HILL, J M The intravenous use of concentrated plasma prepared by the adtevac process, *Texas State Med Jr*, 1940, xxxvi, 223
- (b) HILL, J M, and PFEIFFER, D C A new and economical desiccating process particularly suitable for the preparation of concentrated plasma or serum for intravenous use the adtevac process, *ANN INT MED*, 1940, xiv, 201
- (c) HILL, J M, MUIRHEAD, E E, ASHWORTH, C T, and TIGERTT, W D The use of desiccated plasma, with particular reference to shock, *Jr Am Med Assoc*, 1940, cxvi, 395
- (d) HILL, J M The preparation of desiccated plasma by mass production methods, its importance in routine and military surgery, *New York State Jr Med* (In press)
- (e) HUGHES, JOSEPH, MUDD, S, and STRECKER, E A The reduction of increased intracranial pressure by concentrated solutions of human lymph serum, *Arch Neurol and Psych*, 1938, xxxix, 1277
- (f) BROWN, H A, and MOLLISON, P L A note on the transfusion of reconstituted dried human serum, *Brit Med Jr*, 1940 ii, 821
- (g) RAVDIN, I S, STENGEL, A, and PRUSCHANKIN, M The control of hypoproteinemia in surgical patients, *Jr Am Med Assoc*, 1940, cxiv, 107
- 4 BLALOCK, A, and MASON, M F Blood and blood substitutes in the treatment and prevention of shock with particular reference to their uses in warfare, *Ann Surg*, 1941, cxiii, 657
- 5 (a) MAHONEY, E B The study of experimental and clinical shock with special reference to its treatment by the intravenous injection of preserved plasma, *Ann Surg*, 1938, cviii, 178
- (b) LEVINSON, S O, NEWELT, F, and NECHELES, H Human serum as a blood substitute in the treatment of hemorrhage and shock, *Jr Am Med Assoc*, 1940, cxiv, 455
- (c) BEST, C H, and SOLANDT, D Y Use of plasma or serum as a substitute for whole blood, *Brit Med Jr*, 1940, i, 116
- (d) MAGLADERY, J W, SOLANDT, D Y, and BEST, C H Serum and plasma in the treatment of hemorrhage in experimental animals, *Brit Med Jr*, 1940, ii, 249
- (e) JOHNSON, G S, and BLALOCK, A Experimental shock, a study of the effects of the loss of whole blood, of blood plasma and of red blood cells, *Arch Surg*, 1931, xxi, 626
- (f) BEARD, J W, and BLALOCK, A Intravenous injections, a study of the composition of the blood during continuous trauma to the intestines when fluid is injected continuously, *Jr Clin Invest*, 1932, i, 249
- (g) BUTTLE, G A H, KEKWICK, A, and SCHWEITZER, A Blood substitutes in the treatment of acute hemorrhage, *Lancet*, 1940, ii, 507
- 6 (a) BOND, D D, and WRIGHT, D G The treatment of hemorrhage and traumatic shock by the intravenous use of lymph serum, *Ann Surg*, 1938, cvii, 500
- (b) HILL, J M, ASHWORTH, C T, and MUIRHEAD, E E Unpublished data
- 7 (a) UNDERHILL, F P, KAPSINOW, R, and FISK, M E Studies on the mechanism of water exchange in the animal organism, the nature and effects of superficial burns, *Am Jr Physiol*, 1930, xcv, 302

- (b) UNDERHILL, F P, and FISK, M E Studies on mechanism of water exchange in animal organism composition of edema fluid resulting from superficial burn, *Am Jr Physiol*, 1930, xc, 330
- (c) BLALOCK, A Experimental shock Importance of local loss of fluid in production of low blood pressure after burns, *Arch Surg*, 1931, xxii, 610
- (d) BEARD, J W, and BLALOCK, A Experimental shock composition of fluid that escapes from the blood stream after mild trauma to an extremity, after trauma to intestines and after burns, *Arch Surg*, 1931, xxii, 617
- (e) HARKINS, H N Experimental burns, rate of fluid shift and its relation to onset of shock in severe burns, *Arch Surg*, 1935, xxxvi, 71
- 8 (a) THOMPSON, W D, RAVDIN, I S, and FRANK, I L Effect of hypoproteinemia on wound disruption, *Arch Surg*, 1938, xxxvi, 500
- (b) THOMPSON, W D, RAVDIN, I S, and FRANK, I L Use of lyophile plasma in the correction of hypoproteinemia and prevention of wound disruption, *Arch Surg*, 1938, xxxvi, 509
- (c) RAVDIN, I S Hypoproteinemia and its relation to surgical problems, *Ann Surg*, 1940, cxii, 576
- 9 WHIPPLE, G H, SMITH, H P, and BEET, A E Shock as a manifestation of tissue injury following rapid plasma protein depletion, *Am Jr Physiol*, 1920, lii, 72
- 10 HARKINS, H N, and HARMON, P H Plasma exudation, *Ann Surg*, 1936, cvi, 1070
- 11 (a) GENDEL, S, and FINE, J The effect of acute intestinal obstruction on the blood and plasma volumes, *Ann Surg*, 1939, cx, 25
- (b) FINE, J, and GENDEL, S Plasma transfusion in experimental intestinal obstruction, *Ann Surg*, 1940, cxii, 240
- 12 MADDEN, S C, and WHIPPLE, G H Plasma proteins their source, production and utilization, *Physiol Rev*, 1940, xx, 194
- 13 WRIGHT, D, BOND, D, and HUGHES, J The reduction of cerebrospinal fluid pressure by concentrated lyophile serum, further observations, *Arch Neurol and Psych*, 1938, xxxix, 1288
- 14 (a) WIECH, A A, GOLTTSCH, E, and REEVES, E B The effect of serum transfusion on the plasma protein depletion associated with nutritional edema in dogs, *Jr Clin Invest*, 1933, xii, 217
- (b) WIECH, H H, GOETTSCH, W, and LITTLE, J D Intravenous injection of serum and acacia in the treatment of edema, *Med Clin N Am*, 1940, 807
- (c) JONES, C M, and EATON, F B Postoperative nutritional edema, *Arch Surg*, 1933, xxxvii, 159
- (d) JONES, C M, EATON, F E, and WHITE, J C Experimental postoperative edema, *Arch Int Med*, 1934, lxi, 649
- (e) MUNTWYLER, L, WAY, C T, BINUS, D, and MYERS, V C Plasma protein and plasma colloid osmotic pressure in pathological conditions with special reference to the occurrence of edema, *Jr Clin Invest*, 1933, xii, 495
- 15 (a) WEINER, D O, ROWITT, A P, and ELMAN, R Significance of loss of serum protein in therapy of severe burns *Proc Soc Exper Biol and Med*, 1936, xxxiv, 484
- (b) MCCURR, R D The treatment of a patient with severe burns, *Jr Am Med Assoc*, 1939, cxiii, 1809
- (c) ELLINGTON, J R, WHITE, W A, and LEE, W E Plasma transfusion in the treatment of fluid shift in severe burns, *Ann Surg*, 1940, cxii, 150
- (d) MINOT, A S, and BLALOCK, A Plasma loss in severe dehydration shock and other conditions as affected by therapy, *Ann Surg*, 1940, cxii, 557
- (e) TILSON, H M, GILBERT, H L, and WILLIAMS, H S Burn shock, *Jr Am Med Assoc*, 1939, cxiii, 2207
- (f) COMBS, S M Experience in the treatment of war burns, *Brit Med Jr*, 1940, i, 251

- (g) ALDRICH, C A, STOKES, J, JR, KILLINGSWORTH, W P, and MCGUINNESS, A C Concentrated human blood serum as a diuretic in the treatment of nephrosis, preliminary report, *Jr Am Med Assoc*, 1938, cxi, 129
- (h) ALDRICH, C A, and BOYLE, H H Concentrated human blood serum as a diuretic in nephrosis, further observations, *Jr Am Med Assoc*, 1940, cxiv, 1062
- 16 (a) SHAKILL, L F An improved method of desiccation with some applications to biological problems, *Am Jr Physiol*, 1909, xxiv, 325
- (b) ELSE, W J, THOMAS, R A, and STEFFEN, G T The desiccation of sera and other biological products (including microorganisms) in the frozen state with the preservation of the original qualities of the products so treated, *Jr Immunol*, 1935, xxviii, 433
- (c) FLOSDORF, E W, and MUDD, S An improved procedure and apparatus for preservation of sera, microorganisms and other substances—the Cryochem process, *Jr Immunol*, 1938, xxxiv, 469
- (d) GREAVES, R I N, and ADAIR, M D Simple method for the preservation of sera by desiccation in frozen state without use of refrigerants, *Jr Hyg*, 1936, xxxvi, 507
- 17 (a) FLOSDORF, E W, and MUDD, S Procedure and apparatus for preservation in "lyophile" form of serum and other biological substances, *Jr Immunol*, 1935, xli, 389
- (b) REICHEL, J Mentioned by Flosdorf and Mudd ^{17a}
- (c) GREAVES, R I N, and ADAIR, M D High vacuum condensation drying of proteins from frozen state, *Jr Hyg*, 1939, xxxiv, 413
- 18 FLOSDORF, E W, STOKES, F J, and MUDD, S The desivac process for drying from the frozen state, *Jr Am Med Assoc*, 1940, cxv, 1095
- 19 (a) THALHIMER, W A simple inexpensive method for concentrating serum under sterile conditions, *Proc. Soc Exper Biol and Med*, 1938, xxxvii, 639
- (b) TERRY, M C Artificial concentration of test serum in blood grouping, *Jr Am Med Assoc*, 1939, cxii, 135
- (c) HARPER, S B, ESSE, H E, and OSTERBERG, A E The preparation and experimental use of dried blood plasma, *Proc Staff Meet Mayo Clinic*, 1940, xv, 689
- (d) EDWARDS, F R, KAY, J, and DAVIE, T B The preparation and use of dried plasma for transfusion, *Brit Med Jr*, 1940, i, 377
- (e) AYLWARD, F X, MAINWARING, B R S, and WILKINSON, J F The concentration and drying of plasma, *Brit Med Jr*, 1940, i, 583
- (f) HARTMAN, F W, and HARTMAN, F W, JR Use of cellophane cylinders for desiccating blood plasma, *Jr Am Med Assoc*, 1940, cxv, 1989
- 20 FLOSDORF, E W, and WEBSTER, G W The determination of residual moisture in dry biological substances, *Jr Biol Chem*, 1937, cxvi, 353
- 21 BING, F C, and BAKER, R W The determination of hemoglobin in minute amounts of blood by Wu's method, *Jr Biol Chem*, 1931, 92
- 22 HILL, J M, and MUIRHEAD, E E Unpublished data
- 23 GAMBLE, J L Dehydration, *New Eng Jr Med*, 1929, cci, 909
- 24 COLLIER, F A, and MADDOCK, W G Water balance in surgical conditions, *Internat Clin*, 1934, iii, 190
- 25 KEITH, N M Blood volume changes in wound shock and primary hemorrhage, Medical Research Committee, Special Report Series, No 27, March, 1919
- 26 (a) CANNON, W B Traumatic shock, 1923, D Appleton and Co, N Y
- (b) MOON, V H Shock and related capillary phenomena, 1938, Oxford Univ Press, New York
- (c) PHEMISTER, D B, and LIVINGSTONE, H Primary shock, *Ann Surg*, 1934, c, 714
- (d) PHEMISTER, D B Surgical shock, *Surg, Gynec and Obst*, 1935, lx, 750
- (e) BLALOCK, A Principles of surgical care, shock and other problems, 1940, C V Mosby Co, St Louis

- 27 (a) ROUS, P, and WILSON, G W Fluid substitutes for transfusion after hemorrhage, Jr Am Med Assoc, 1918, lxx, 219
- (b) AMBERSON, W R Blood substitutes, Biol Rev, 1937, xii, 48
- 28 (a) BUTLER, A M Electrolyte and water balance, New Eng Jr Med, 1939, ccxx, 827
- (b) ADOLPH, E F, GERBASI, M J, and LEPORÉ, M J Redistributions of water following transfusions and infusions, Am Jr Physiol, 1934, cvii, 647
- (c) KING, R A Methods of fluid administration in the treatment of surgical shock an experimental comparison, Brit Med Jr, 1940, ii, 485
- (d) BOYCOTT, A E On the regulation of the blood volume in normal and nephrotic animals, Jr Path and Bact, 1913, xviii, 11
- (e) SMITH, A R, and MENDELL, L B The adjustment of blood volume after the injection of isotonic solution of varied composition, Am Jr Physiol, 1920, liii, 323
- 29 (a) KROGH, A, and HARROP, G A On the substance responsible for capillary tonus, Jr Physiol, 1921, liv, 125
- (b) DRINKER, C K The permeability and diameter of the capillaries in the web of the brown frog (*R Temporaria*) when perfused with solution containing pituitary extract and horse serum, Jr Physiol, 1927, lxxiii, 249
- 30 SCUDDER, J Shock, blood studies as a guide to therapy, 1940, J B Lippincott Co, Philadelphia
- 31 References under 7
- 32 Discussion by Bucy of article by Hughes, Mudd and Strecker³⁰
- 33 (a) Minimum requirements for unfiltered normal human plasma, Pamphlet by National Institute of Health, Feb 20, 1941
- (b) VELDEE, M V, Chief of Division of Biologic Control, U S Department of Health Service, National Institute of Health (Personal correspondence)
- 34 SFIERT, F B Fever producing substances found in some distilled waters, Am Jr Physiol, 1923, lxxvii, 90
- 35 (a) OTTENBERG, R, and FOX, C L, JR The rate of removal of hemoglobin from the circulation and its renal threshold in human beings, Am Jr Physiol, 1938, cxliii, 516
- (b) GILLIGAN, D R, ALTSCHULE, M D, and KATERSKY, E M Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions, Jr Clin Invest, 1941, xx, 177
- (c) DE NAVAQUEZ, S The excretion of hemoglobin, with special reference to the "transfusion" kidney, Jr Path and Bact, 1940, li, 413
- (d) SHILARDS, A W, and MINOT, G R Injection of hemoglobin in man and its relation to blood destruction, with especial reference to the anemias, Jr Med Res, 1916, xxxiv, 469
- (c) FAIRLEY, N H The fate of extracorporeal hemoglobin, Brit Med Jr, 1940, i, 213
- (f) AMBERSON, W R 27b
- 36 THALHIMER, W Personal communication
- 37 (a) ADOLPH, E F, and LEPORÉ, M J Blood pressure as a chief factor modifying the water content of tissues, Am Jr Physiol, 1931, xcvi, 501
- (b) ADOLPH, E F, GERBASI, M J, and LEPORÉ, M J The rate of entrance of fluid into the blood in hemorrhage, Am Jr Physiol, 1933, civ, 502
- 38 BLACK, D A K, and SMITH, A F Blood and plasma transfusion in alimentary hemorrhage, Brit Med Jr, 1941, i, 187
- 39 GOSWELL, J L Chemical anatomy, physiology and pathology of extracellular fluid, a lecture syllabus, 1939 Department of Pediatrics, The Harvard Medical School
- 40 (a) FREEMAN, N E, and WALLACH, W M The effect of concentrated serum or plasma on plasma volume and serum protein concentration, Am Jr Physiol, 1938, cxvii, 791
- (b) HILL, J M, MUIRHEAD, F E, ASHWORTH, C T and WATERS LEWIS Dedicated plasma exhibit A M A Meeting Cleveland June 1941 Scientific Exhibit at the 1940-1941 Annual Session of the American Medical Association

OBSERVATIONS ON THE SPECIFIC TREATMENT (TYPE A ANTISERUM) OF STAPHYLOCOCCAL SEPTICEMIA; SECOND REPORT *

By L A JULIANELLE, *St Louis, Missouri*

IN an earlier communication¹ published in this journal, a preliminary account was given of the experimental treatment of staphylococcal septicemia with specific antibacterial serum. Obtained from rabbits following immunization with intact, formalinized organisms, the antiserum was particularly prepared to contain high titers of antibody capable of reacting with the somatic carbohydrate extractable from pathogenic (Type A) staphylococci.² The rationale for the therapeutic expectancy of such an antiserum was based on the theoretical considerations arising from the observation that precipitins for the carbohydrate in question are demonstrable in the sera of those patients only who have recovered from severe, generalized infection.³ Although it was obviously impossible to arrive at an appraisal of the antiserum in the preliminary report, the results were sufficiently encouraging to warrant a more extended study on the therapeutic effectiveness of the Type A, anticarbohydrate serum. This has now been done, since in the interim 98 unselected patients with genuine staphylococcal septicemia and four with severe infection and unverified septicemia have received the serum as the basic treatment during their courses of infection. While it may be argued that even this number perhaps fails to supply the statistical basis eventually desired, it is nevertheless true that the series is now large enough to establish the principles involved and to suggest at least a potential value for such an antiserum.

METHODS OF STUDY

Type A Antiserum The antisera under study were all prepared in rabbits, originally in this laboratory as described elsewhere,¹ for use in the first 32 patients. Later, both the Lederle Laboratories of Pearl River, N Y, and the Eli Lilly Co, of Indianapolis, furnished sera prepared and standardized under the writer's direction, and more recently, in fact, the former organization not only incorporated certain modifications in production, but has since evolved purified and concentrated preparations. It may be said at this point, however, that in so far as anticarbohydrate titer and therapeutic efficiency are concerned, each of the three laboratories prepared successful antisera.

Selection of Patients No attempt has been made to select patients. Calls for serum were answered by priority irrespective of the patient's age, clinical condition or complication, duration of the infection, prognosis, etc.

* Received for publication July 11, 1941

From the Department of Ophthalmology, Washington University School of Medicine, St Louis

Conducted under a grant from the Commonwealth Fund of New York

The only restriction imposed was that each patient must have had at least two positive blood cultures on consecutive days before administration of serum. Further details concerning the patients studied, however, will be discussed more appropriately later in this report.

Administration of Antiserum Before giving serum in therapeutic doses, it was necessary to test each patient's sensitivity to the serum. This was accomplished by determining the effect of the serum on blood pressure, pulse rate, and respiration. A mixture of 1 c c of serum in 10 c c of saline was injected slowly by the intravenous route, and the patient was watched over a period of about one hour. If within that time no significant changes occurred in blood pressure (reduction of 15 mm or more), pulse rate (increase of 15 beats or more per minute), or respiration, serum treatment was then started. It may be said at this point that in no individual was this test in the least harmful. In each case it was possible to start serum in therapeutic doses, although in several because of various reactions (urticaria, respiratory difficulty, increased pulse rate, etc.) the administration had to be interrupted and either continued intravenously later, or from then on only by the intramuscular route. In the latter case, 10 to 20 c c of serum were repeated at intervals of four to six hours. In the end, the route of administration apparently played no important part, obviously more time is required to raise the antibody blood level to an effective point by the intramuscular route, but having once been reached, antibody concentration may readily be maintained by this method.

Determining the initial quantity of antiserum to be administered has been a difficult matter, because several factors, some definitely obscure, enter into the dosage. Since the infection, not the age nor sex of the patient, is to be combated, an attempt has been made to estimate the dosage of serum according to the degree of infection. Thus, the number of staphylococci per c c of blood, duration of infection, rapidity of spread, distribution and extent of metastases were all considered. Consequently, the initial dosage was varied from 60 c c to 120 c c of serum. As will be described, this was frequently followed by further administration on successive days as deemed necessary.

In giving the serum, it was always diluted at least once with saline, Hartmann solution, or Ringer's solution. The mixture was introduced slowly by gravity and if untoward symptoms developed, the injection was immediately stopped and adrenalin was used, sometimes supplemented by caffeine or some other stimulant.

Index of Adequate Serum Therapy In order to determine when sufficient serum had been given, skin tests were performed with the carbohydrates derived from staphylococci. That from Type A was used for the actual test and that from Type B (non-pathogenic) for purposes of control. The carbohydrates were used in dilutions of 1:100,000 of which 0.2 c c was injected intracutaneously. A positive reaction manifested itself within a few

minutes by a wheal and erythema, as described in the earlier report. Thus, the appearance of such a reaction was interpreted as indicating an excess of antibody in circulation and, therefore, that further administration of serum would be superfluous. Granted that in some individuals with highly reactive skins, reactions may be difficult to interpret because of their non-specificity, such examples, nevertheless, are decidedly in the minority and it may be said that in every case exhibiting a genuine reaction to Type A carbohydrate, recovery inevitably followed.

The following routine was, therefore, adopted in performing skin reactions. Skin tests were done on each day of serum treatment including the first day. Preferably 20 to 24 hours should have elapsed since administration of serum before injecting carbohydrates. This is an important precaution because it has been found that immediately following introduction of serum the skin reacts avidly with homologous carbohydrate, in some instances within an hour to an hour and a half following cessation of serum. This is more often than not, however, merely a transient reactivity to be dissipated completely by the following morning. If, then, after about 24 hours the skin test elicits a strong reaction, serum therapy is discontinued, while lack of any reaction or even a moderate reaction implies that more serum should be given. Again the dosage is arrived at by several considerations, but in general 40 to 60 c c make an average quantity. The procedure of daily skin test and additional serum is thus continued until the development of a strongly positive reaction.

If skin reactivity to Type A carbohydrate cannot be determined, because carbohydrates are not available, or because of lack of experience with the vagaries of skin reactions, a less accurate, but more or less satisfactory index of further serum administration may be deduced from the patient's general condition, the temperature chart, and the blood culture. To accelerate results in the last case, it is recommended that blood be cultured directly in agar plates, since with clinical improvement growth in broth may be delayed as long as three and four days.

Supportive Treatment All the patients in this group received whatever supplementary treatment was indicated. Thus, transfusions were given when the red blood count fell to 3,500,000 cells per cu mm. Surgical care was considered of utmost importance and, as far as the writer is concerned, on a par with serum therapy itself. It must be remembered that staphylococci not only cause localized abscesses, but possess a considerable capacity for tissue destruction, eventuating in replacement with scar tissue. Consequently, unless the abscess is forced to evacuate outwardly, it may well discharge inwardly, thus frequently reaching the circulation. Moreover, unless adequate drainage is established all those toxic by-products liberated by the destroyed tissues can be eliminated only by absorption, obviously adding to the general toxemia, even assuming that the bacteria themselves have been effectively suppressed. It is, in fact, the opinion of the writer that staphylo-

coccal septicemia is as much a surgical as a medical emergency, and for effective management the condition requires complete collaboration of surgeon and internist or pediatrician

What surgical procedures were to be adopted in this study were left for the surgeon in charge to decide. In a general way, however, it seemed wiser not to intervene in the spreading cellulitis or edematous type of infection and to delay operative procedures until the lesion began to localize, whether the lesion was of the bony or soft tissues. It is realized, of course, that opinion is divided on the proper course in such cases, so that it may be dangerous to dogmatize. The impression has been gained in this study that the use of serum before operation, particularly in cases of osteomyelitis, is a prophylactic measure of value, and for this reason this procedure was frequently adopted in later patients.

At this point it may be well to add that where sulfonamides had been part of the treatment before serum was used, the drugs were promptly withdrawn. It was discovered later, however, that in certain cases the drugs were continued, but such instances formed a very small minority, and it is felt that the infection was not materially influenced by the additional treatment.

Collateral Bacteriological Studies During the course of treatment daily blood cultures were made, in most cases by plating 10 cc and 20 cc of blood and by inoculating broth with 50 cc or more of blood. The plates were incubated, in general, for 48 hours before making final estimation of the number of colonies per cc of blood, while the broth cultures were incubated for one week before being discarded as sterile. In certain infrequent instances, however, it was not possible to carry through this procedure. Where drainage was instituted, cultures of the escaping pus were made on infusion blood agar plates so that the strains from the localized lesions might eventually be compared with those originating from the blood. Each strain was tested for its ability to ferment mannite, since typical pathogenic cultures produce acid in this sugar,¹ and the organism was subsequently classified by the carbohydrate extracted from it. In addition, each strain was measured for virulence in white mice, and more than half were tested in rabbits as well. Random strains were also inoculated in guinea pigs.

Analysis of the bacteriological information reveals that practically each patient had at least three daily positive blood cultures before the administration of serum. As will be shown later (table 4) there were four exceptions to this rule.

Variations in the numerical count of colonies covered a range of several thousand colonies per cc of blood, as will be brought out later. Every strain tested fermented mannite, in an occasional culture, however, fermentation was delayed to the third or even fourth day. In each case Type A carbohydrate was extracted from the bacterial cell. Comparison of the strains from localized pus and blood cultures disclosed no variations in the

tests conducted, suggesting, therefore, that the organism in the blood had actually penetrated from the external focus

Tests for virulence in the different animals were highly disappointing, since it was hoped that an animal-virulent strain would sooner or later be encountered. Death was induced only by excessively large numbers of organisms and the results were extremely irregular. Thus, some cultures killed white mice in dosages of 0.1 c.c. (ca. 50 million organisms) and rarely 0.01 c.c. (ca. 5 million organisms) of young broth cultures injected intraperitoneally or intravenously, but the results could not be duplicated with any degree of regularity. Many cultures, even in dosages of 0.5 c.c. or 1.0 c.c., had little effect on any of the three animals (mouse, rabbit, guinea pig). If it is recalled that the organism tends toward the classical formation of clusters, it will be realized that when death does occur following the injection of large dosages, the fatality may be as much the result of capillary emboli as of actual infection. In any case, it is extremely difficult to measure in the commoner animals the virulence of strains derived from man, even when the infection is fatal.

CLINICAL OBSERVATIONS

As stated earlier, 102 patients have now been treated with antistaphylococcal, Type A rabbit serum. This number represents a great variety of disease, with patients ranging in age from four months to 72 years. The largest group was composed of cases with acute osteomyelitis complicated with septicemia, there being a total of 26 such examples. The next largest group included cases with heart involvement (15 with endocarditis and three with pericarditis) and a third group of nearly the same size was made up of cases of furunculosis (14 cases). The other individuals represented a scattering of clinical conditions as the predominant factor in the infection, such as primary pneumonia in eight, sinus thrombosis and meningitis in three, septicemia following abortion in three, etc., etc. In other patients the staphylococcal septicemia was aggravated by diabetes (difficult to control in five), sulfanilamide poisoning with severe leukopenia in two, congenital jaundice in two, tuberculosis of the spine and dissecting aneurysm in one, pemphigus foliaceus in one, leukemia in one, malnutrition (in an infant), one, Cushing's syndrome, one, arsphenamine poisoning with extensive hepatic damage in one, nephrosis, one, and internal hemorrhage due to an injury in one. Of the total series, 62 were treated in St. Louis, 18 in various places throughout the country, and 22 at the Philadelphia General Hospital. The third group is being published separately from that institution⁵ but will be reviewed summarily here to render the analysis as complete as possible.

Of the 102 patients treated as described, 48 survived and 54 died. In order to present the data simply and comprehensively, it is proposed to submit a separate analysis of the fatal and non-fatal cases.

SYNOPSIS OF PATIENTS RECOVERING

Before entering upon a description of the individuals considered as successfully treated with Type A serum, it may be relevant to illustrate by clinical observation the specificity of the antistaphylococcal serum

CASE REPORT

Case 83 A white female, 34 years of age, entered the hospital with extensive pemphigus foliaceus of three months' duration. After six weeks' hospitalization during which the skin condition became intensified rather than diminished, the patient developed a septic temperature which was soon proved to be due to a septicemia caused by hemolytic *Staphylococcus aureus* of the mannite-fermenting, Type A variety. The first three daily blood cultures were pure growths of staphylococcus,

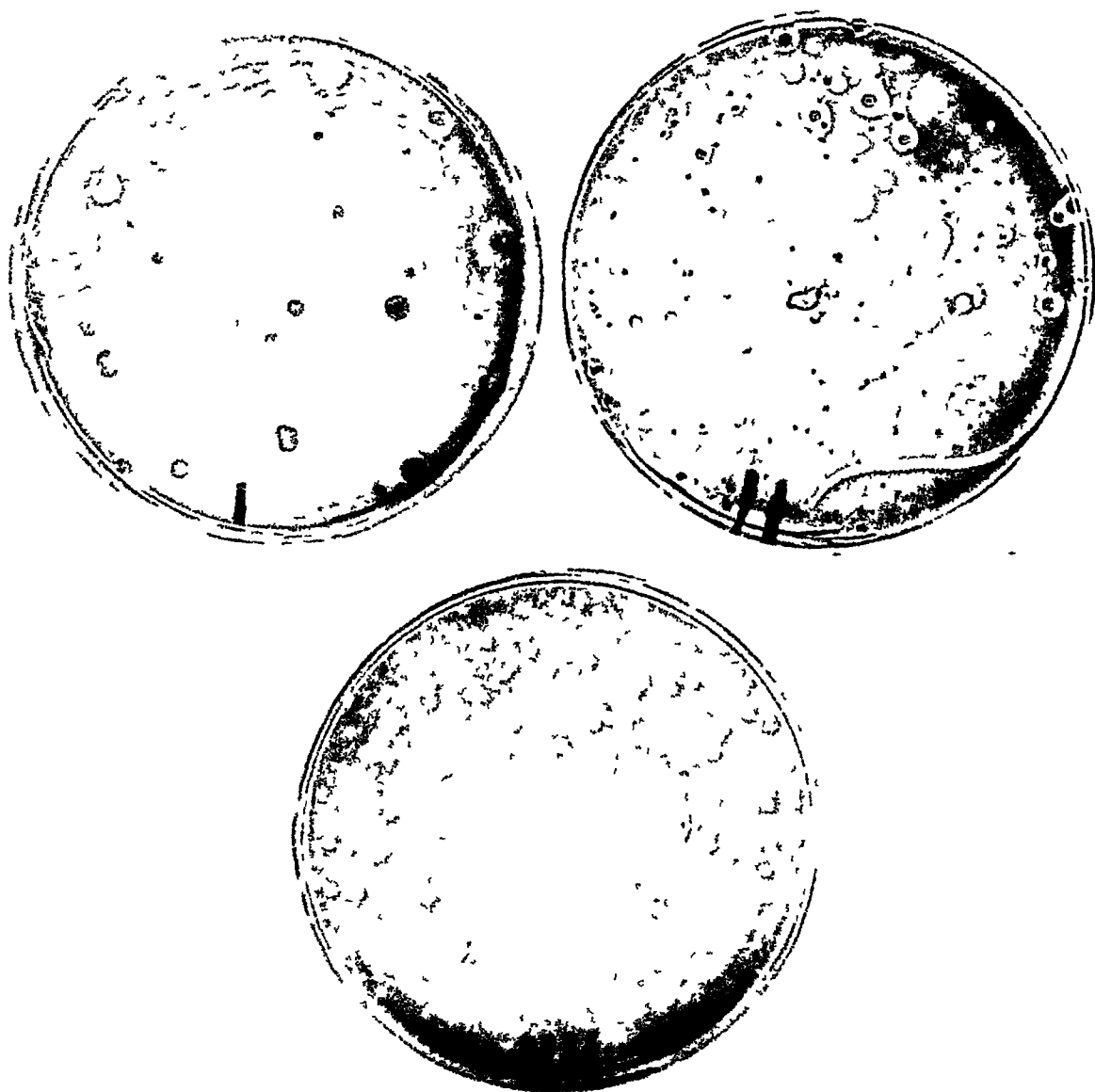


PLATE I. Specificity of Type A Antiserum. Photographs of blood culture plates made on first, fourth and seventh days of septicemia. Upper left, pure staphylococci, upper right, staphylococci and streptococci, lower, staphylococci eliminated—pure culture of streptococci (remains fluid test).

but on the fourth day, with the number of colonies of this organism definitely receding, the plates were noticed to contain several colonies of hemolytic streptococci. Administration of serum which had been started on the second day was accompanied by a complete disappearance of the staphylococci by the fifth day of septicemia (third day of treatment), while in the same period the number of streptococcal colonies distinctly increased. From then on the blood stream remained free of staphylococci. The patient was given sulfanilamide in large doses in an effort to check the streptococcus invasion but without avail. The blood culture was consistently positive for this organism for some two weeks, towards the end, in fact, the cultures showed mixed growths with diphtheroids and colon bacilli which were probably due to the technical difficulty of obtaining uncontaminated blood, because of the condition of the skin. At postmortem examination, no metastatic abscesses were detected, and a vegetative endocarditis on the tricuspid valve yielded a pure growth of streptococci. This is considered a remarkable example of the specificity of the antiserum, further evidence of which has been obtained experimentally and will be presented at a future date. In order to illustrate the forerunning observations, photographs (plate 1) are given of three blood cultures obtained on the first, fourth, and seventh days of septicemia.

The patients represented among the recoveries were well distributed as to age and clinical manifestation. The ages varied from 18 months to 56 years and the primary foci divided themselves as will be seen in table 1, as follows: osteomyelitis, 24, furunculosis, seven, primary pneumonia, four, localized abscess following trauma, two, infected blister of heel, two, infected pimple of face, two, self-induced abortion, two, undetermined, one, meningitis, three, and frontal sinusitis with osteomyelitis, one.

TABLE I
Summary of Patients Surviving Classified by Initial Infection

Total number of patients treated	102
Total number of patients surviving	48
Osteomyelitis *	24
Furunculosis	7
Pneumonia †	4
Localized abscess following trauma	2
Infected blister of heel	2
Infected pimple of face	2
Endometritis (self-induced abortion)	2
Undetermined	1
Primary meningitis	3
Frontal sinusitis with osteomyelitis	1
Total	48

* The evidence suggests that three patients with pneumonia and one with osteomyelitis did not have septicemia.

† In addition to the primary pneumonias listed, there were 10 examples of metastatic pulmonary infection.

It should be stated in this connection that one of the patients with osteomyelitis had a transient bacteremia rather than septicemia, and of the four patients with pneumonia only one can be certified as having septicemia. In addition to septicemia there were numerous other metastatic complications as

pneumonitis or lung abscesses in 10, with pleurisy or empyema in four of these cases, abscesses of the kidney, four, panophthalmitis, three, iritis with hypopyon, one, sulfanilamide poisoning with agranulocytic leukopenia (white cell count, 800), one, etc Of the 24 cases of osteomyelitis it was felt that nine had no metastatic spread of infection Thus, it is seen that as far as is possible the distribution of patients is typical of staphylococcal septicemia with perhaps a larger than average share of osteomyelitis

Effect of Antiserum on Temperature It may be of interest to describe the effect of the antiserum on the patient's temperature The dramatic drop in fever associated with crisis was observed only rarely In three cases the temperature actually fell to normal overnight and remained close to that point until complete recovery In two of the three patients, the temperature subsequently arose again In one case this occurred after seven days, the fever of 2° F being due to a panophthalmitis which was present early during the septicemia With enucleation, the temperature promptly fell to normal and remained so throughout the patient's stay in the hospital In the second instance, a rise of about 2.5° F was associated with pleurisy with effusion After paracentesis the fever disappeared and the effusion did not recur

As illustrative of this type of effect of serum therapy on fever a summary of case 42 is here cited and the temperature chart reproduced (figure 1)

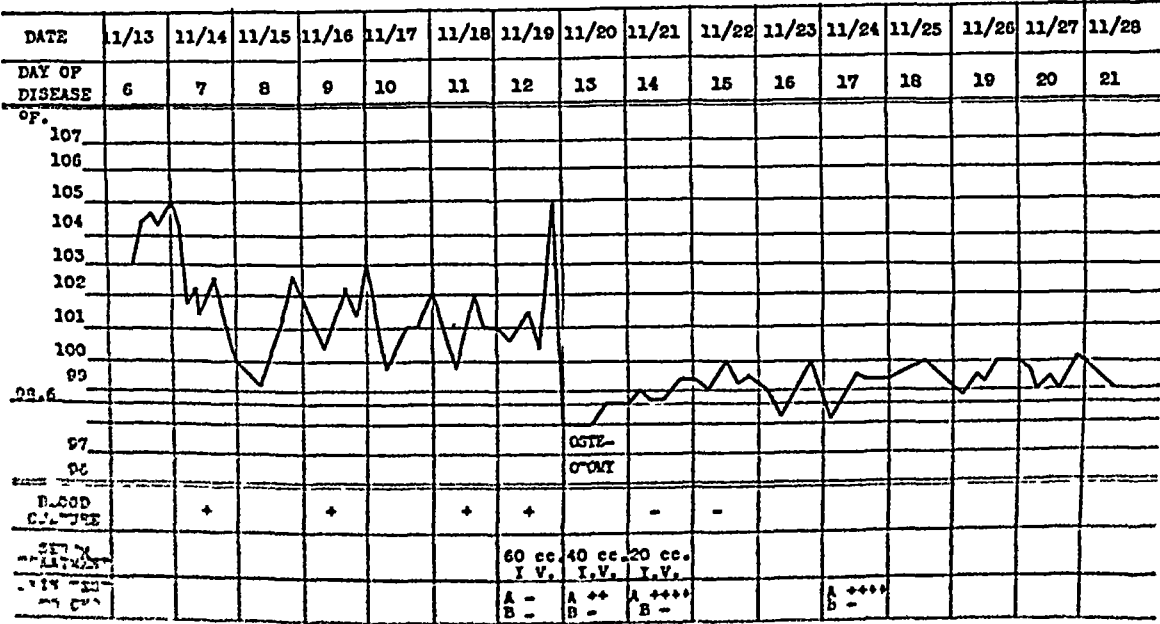


FIG. 1. Effect of Antiserum on Temperature. A Fall by Crisis. In this and succeeding charts minus signs represent test performed was negative, while plus signs indicate an arbitrary degree of positiveness. The numerals given under blood culture are number of colonies per cc. of blood.

Case 42. D. P., a white boy, 11 years old, entered the hospital on the sixth day of illness which started with sudden, unaccountable pain in the left shoulder. On admission he was acutely ill, cyanotic and feverish (103° F). Physical examination revealed frequent extracostal, lobular pneumonitis, and what was considered to be

osteomyelitis of the left shoulder. Blood cultures yielded hemolytic *Staphylococcus aureus*, and on subsequent osteotomy of the humerus, performed after the first injection of serum, the same organism was isolated. Both the bone and pulmonary infections were confirmed by roentgenographic study. The first injection of serum (60 c c intravenously) caused first a thermal rise and then a fall to normal. Because the skin test to carbohydrate was only partially positive, 40 c c of serum were given on the second day, and finally 20 c c on the third day. The chart demonstrates the rapid change brought about by the first introduction of serum.

In the large majority of patients recovering, however, the fall in temperature was more characteristically by lysis. Thus, the daily maximum and minimum temperatures dropped progressively so that a curve drawn halfway between each point for each day shows almost a straight line descending to normal and requiring from four to six days to reach that point.

The character of such a curve is represented in figure 2 and the history of the patient summarized.

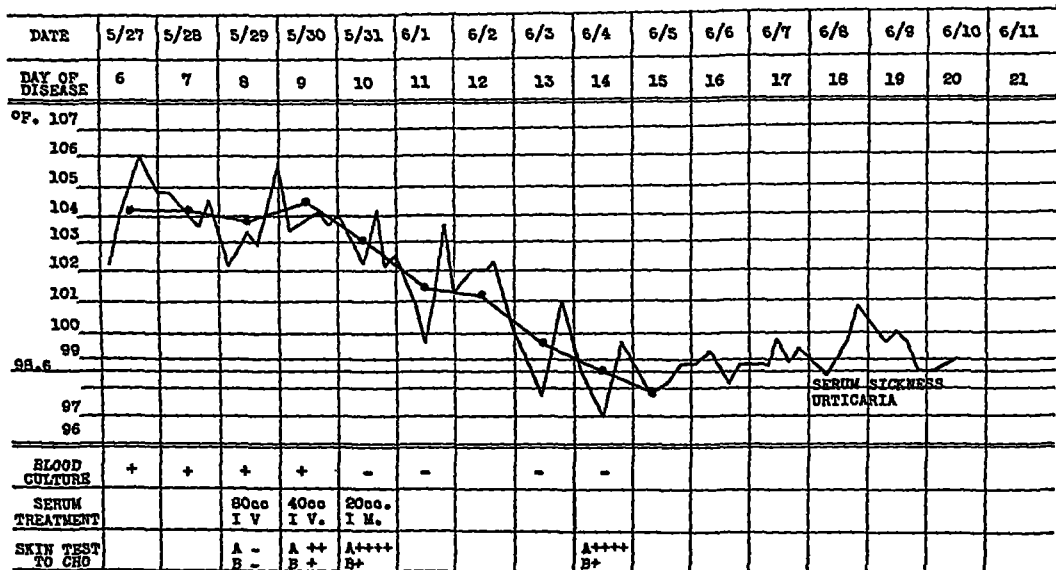


FIG 2 Effect of Antiserum on Temperature B Fall by Lysis Curve with black circles represents average daily temperature Note progressive, daily fall

Case 61 A white boy of 8 years entered the hospital on the sixth day of illness which followed an injury to the right knee. The clinical diagnosis of osteomyelitis of the femur was later verified by roentgen-ray films. The periosteum was incised immediately and a drain was inserted. On the eighth day of illness following two successive, positive blood cultures, 80 c c of serum were administered intravenously. The following day with the skin reaction to carbohydrate only partially positive, 40 c c more were given, also intravenously, and finally 20 c c intramuscularly on the third day. With two serum treatments, the blood culture became sterile, the skin reaction became strongly positive, and the temperature was on the downward trend, requiring six days before maintaining a normal range. Ten days following the first injection of serum there was a rise in temperature due to serum sickness, consisting of extensive urticaria which responded to symptomatic treatment within two days.

Occasional temperature graphs, on the other hand, may still show after serum therapy a more or less sustained fever This type of reaction has been interpreted as suggesting the presence of foci of infection requiring drainage

The following case offers a good example of this variety of fever (figure 3)

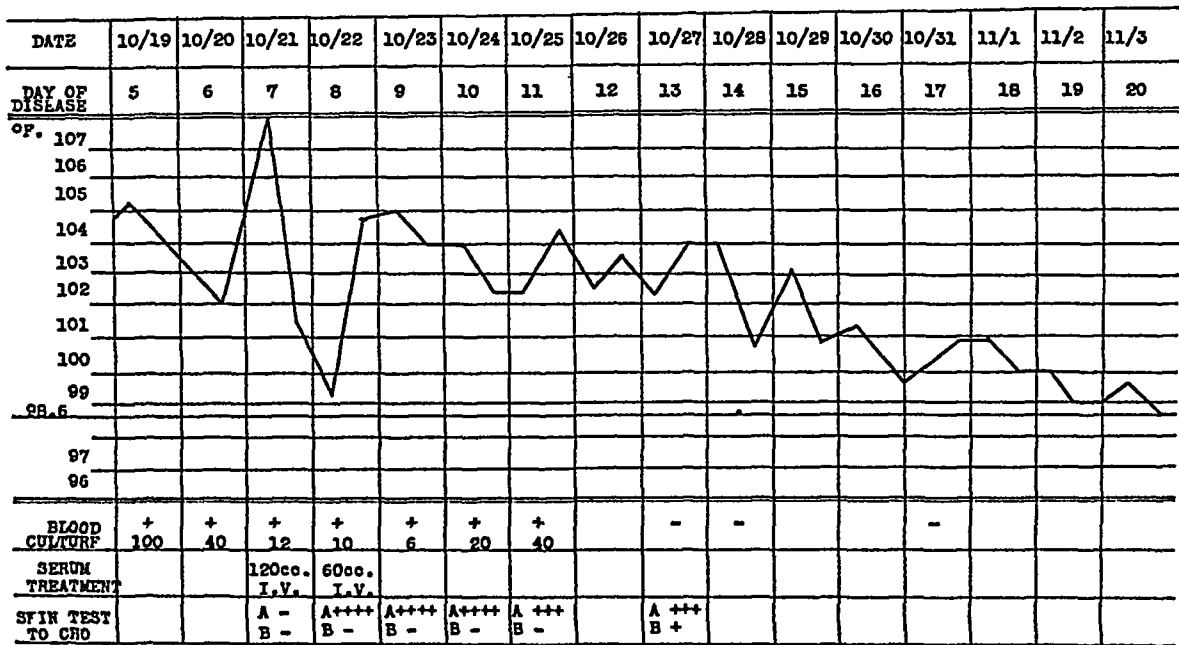


FIG 3 Effect of Antiserum on Temperature C Interference by Foci Requiring Drainage

Case 77 A white boy, 12 years old, was admitted on the third day of illness following a furuncle over the left scapular region, which had been squeezed two days previously The chief clinical signs were obvious spread of infection to both lungs, in addition to septicemia Serum was given on the seventh day, 120 c c intravenously, and on the eighth day 60 c c Additional serum was considered unnecessary because of the strong reaction to Type A carbohydrate It will be noticed (figure 3) that the temperature, nevertheless, remained high for five more days, and then gradually returned to normal This is interpreted as signifying foci of infection (in both lungs) which required drainage, but because of their anatomical distribution were surgically inaccessible Therefore, as long as natural drainage (i e, absorption) went on, the temperature remained high

Such examples add weight to the statement made above that when widespread metastases cause necrosis of tissues releasing toxic substances into the circulation, it is inevitable that the temperature should not be greatly affected by the serum

Effect of Antiserum on Septicemia It should be made clear that while bacteremia implies a transient passage of bacteria in the blood stream, septicemia implies either their constant presence or even their actual growth in the circulation, although not of the order of multiplication observed in vitro In the case of staphylococcus the tendency to abscess formation with eventual extension beyond the abscess wall of the abscess contents leads to frequent bacteremia Consequently, septicemia may be determined only by

frequently repeated blood cultures. It seems important to point out that the number of colonies per c c of blood does not carry the significance that a similar analysis does, say in pneumococcal infection. A study of hundreds of blood cultures made in this laboratory in connection with this investigation indicates clearly the enormous variation in colony counts and the frequent difficulty of reconciling them with the general clinical condition. Thus, in cases of endocarditis, the colony counts sometimes reach into the thousands, while in multiple lung abscess with massive destruction of pulmonary tissue the count may be very low or the blood may even be sterile, despite rapidly ensuing death. The frequent eruption of showers of organisms from local foci into the blood stream, and, conversely, the "filtration" of staphylococci

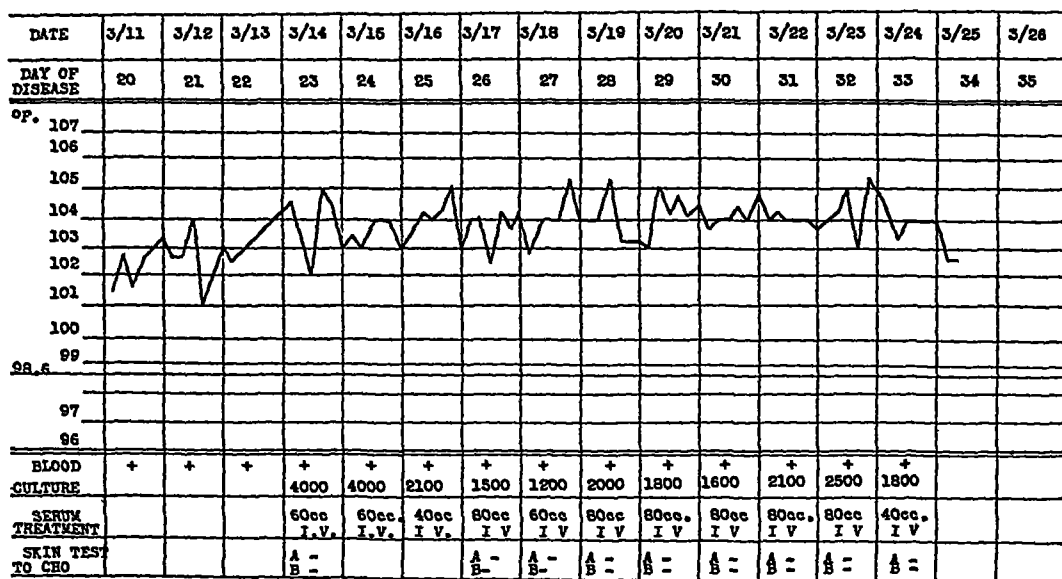


FIG 4 Effect of Antiserum on Temperature D Inefficacy in Endocarditis

by various organs and their artificial removal as capillary emboli in part due to their characteristic formation, may both cause marked variations in numbers which are difficult to reconcile with the general physical condition. Consequently, it is felt that information supplied by colony counts, unless these are uniformly progressive or approximately constant, may be misleading. In any case, it becomes pertinent to analyze the changes in septicemia accompanying the administration of antiserum.

As in the case of the temperatures described above, only a rare patient exhibited sterilization of the blood with a single injection of serum. The large majority of patients recovering required from two to four days or even more (figure 3), before attaining sterile blood cultures, and the colony counts made day by day were usually of the progressively decreasing variety. In order to illustrate sterilization of the blood in a particularly heavy septicemia, photographs of successive blood cultures are submitted in plate 2. This example was not selected as typical, since most septicemias do not reach

such a high point in colony count, but it is submitted as a demonstration of the potential clearing capacity of the serum, even though the case is unusual. Thus, it will be seen that a culture taken immediately before administering antiserum yielded *ca* 400 colonies per c.c. of blood, on the next day preceding a second injection of serum, the count fell to 55 colonies, on the third

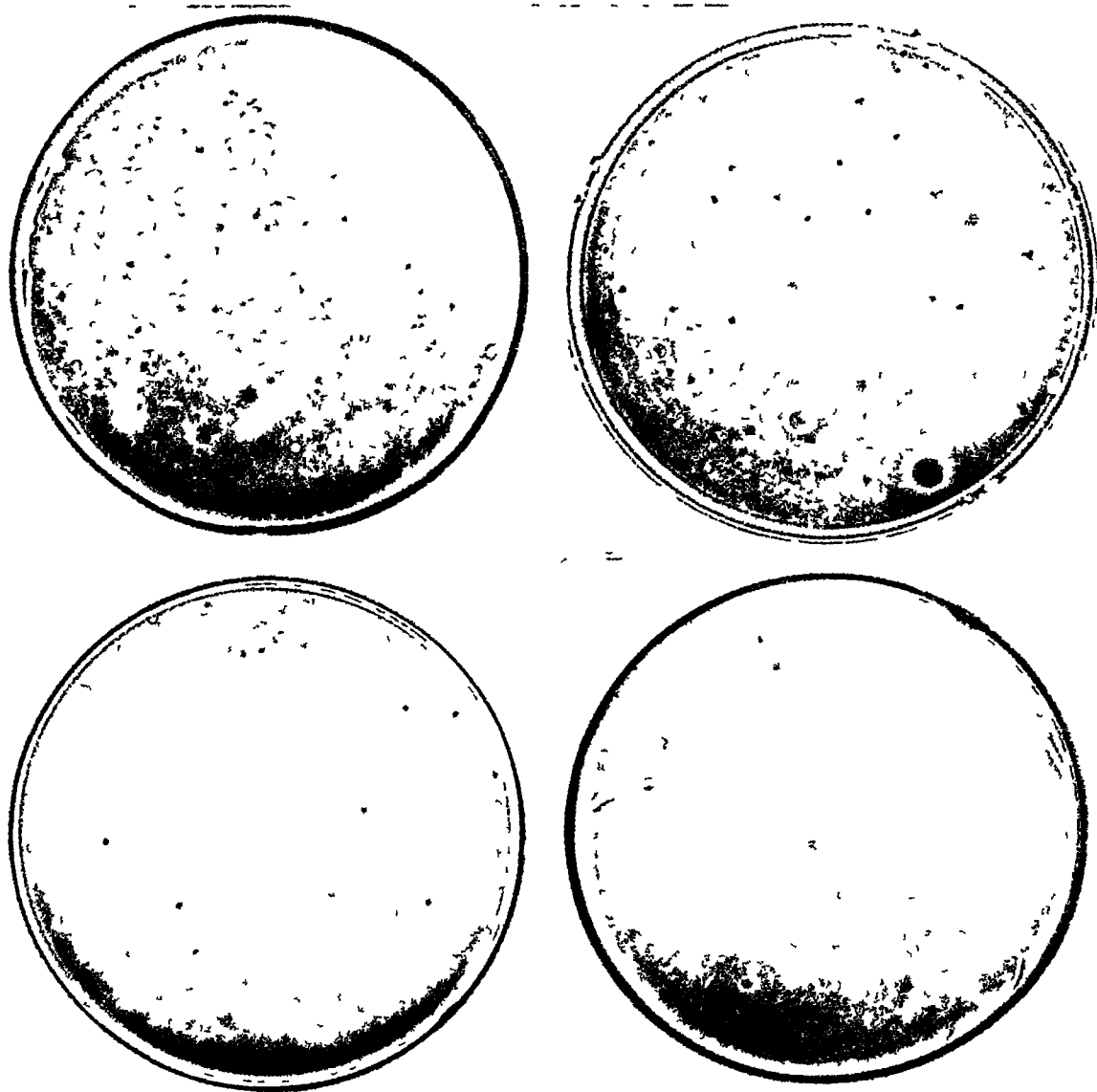


PLATE 2 Effect of Serum on Septicemia. Photographs of blood culture plates (1 c.c. of blood) made on successive days during serum treatment. Upper left, immediately before first administration, over 400 colonies; upper right, immediately before second administration, 55 colonies; lower right, immediately before third administration, 20 colonies; lower left, immediately before fourth administration, nine colonies (*cf.* text).

day preceding more serum, the count fell further to 20 colonies, on the fourth day, before giving the last injection of serum, the count fell to nine colonies, and on the fifth day (after four injections of serum) the blood became sterile.

Effect of Antiserum on Skin Test to Specific Carbohydrates Before starting serum therapy, skin reactions to the carbohydrates were not elicited

in any of the patients tested. While skin reactions to Type A polysaccharide may be demonstrated within an hour to an hour and a half following serum administration (which indicates how rapidly the antibody is distributed in the tissues), this was considered as transient and, therefore, unimportant from the aspect of recovery. Consequently, the skin reactions to be discussed are referable to those appearing 20 to 24 hours after giving serum. On this basis, it has been found that genuine reactions developed after two to four introductions of serum and occasionally the reaction obtained following the first treatment with serum was of sufficient intensity to indicate that further serum administration was unnecessary. When the reaction was once strongly positive the patients went on to recovery. It is interesting to add that thus far the skin reaction to Type A carbohydrate has not failed in its accepted interpretation (i.e., a measurement of immunity). As will be brought out later, the skin tests performed on the patients who died never elicited a skin reaction that could be regarded as definite. Occasionally, the reaction was actually classified as one plus, or even two plus, but this was obviously transient and due to the large quantities of recently administered serum.

Effect of Antiserum on Localized Lesions In treating septicemia by intravenous or intramuscular application of antiserum a careful watch was kept on the different foci of infection. As a generalization it may be said that the antiserum exerted little activity on the original sites of infection, nor, as far as could be determined, on metastatic lesions. Several striking exceptions, however, were noted. Thus, in case 36, a white female, 23 years old, whose septicemia followed the pricking of a small abscess on the upper lip with an unsterilized sewing needle, there was massive swelling of the left face with edema of the lids, iritis, and metastatic pneumonia. Three separate abscesses developed in the iris, which the ophthalmologist in consultation considered sufficient grounds for enucleation. Simultaneously with serum therapy, given over five successive days, the abscesses receded with ultimately complete return to normal. In a second patient, case 13, a white male, 25 years old, whose septicemia followed the placing of gummed mending tape over a cut on the chin caused while shaving, the abscess caused tremendous swelling of the face and neck, and, subsequently, metastatic pneumonia. With serum treatment given on four consecutive days, the face and neck improved remarkably from day to day. The final example was a patient (case 50), a white female, 14 years old, whose septicemia followed by 24 hours a cut on the lower lip inflicted by a dentist's drill. She developed metastatic pneumonia and massive swelling and discoloration of the face and neck. Two administrations of serum were accompanied by sterilization of the blood, and definite, but not complete recession of the facial infection. In the pneumonic infections also serum therapy apparently caused a certain degree of improvement as evidenced by roentgenograms, but the changes were not as conspicuous as the preceding examples, and healing went on for

considerable time after serum had been discontinued. Consequently, the writer has not been greatly impressed with the effect of the serum on the localized lesions and therefore, desires to emphasize again the great importance of utilizing surgical measures to create optimum conditions for accelerated and complete healing.

That the antiserum may have a preventive action on the formation of metastatic abscesses will be discussed later. Since the evidence for this opinion is best furnished by postmortem examination, it seems more appropriate to consider this point as part of the report on the fatal cases. At this point, however, attention may be drawn to the summary of case 83 (*vide supra*), which suggests the lack of metastatic infection accompanying the use of Type A antiserum.

Serum Reactions. This report would not be complete without a word of summary regarding the reactions induced by the antiserum. As stated early, the intravenous trial dose given preliminarily to therapeutic administration was tolerated without difficulty by all the patients. In rare individuals, the first therapeutic injection had to be discontinued because of some troublesome reaction, as urticaria, respiratory difficulty, or decreasing pulse rate. This has already been alluded to above and need not be repeated here. In a certain number of patients, however, the symptom-complex recognized as serum sickness was also observed. Thus, in the 48 survivals, 17 (*ca* 35 per cent) gave evidence of this complication. In each case there was a varying degree of urticaria, in some combined with edema, and in two patients, with arthritic pain and swelling. Serum sickness came on within nine to 14 days following the use of serum; it usually lasted 24 hours, occasionally 48 hours, and it always responded promptly to symptomatic treatment.

In this connection an anomalous reaction worthy of note was encountered which has been difficult to classify. A boy of 15 years, with acute osteomyelitis of the left upper tibia was given 60 c.c. of serum intravenously on the day following osteotomy. After a thermal rise of 2 or more degrees to 105° F., the temperature began to fall, and within 16 hours after the injection the temperature reached 95° F., where it remained for four hours. Finally, after various unsuccessful measures, an enema of hot, concentrated coffee was given, and whether because or in spite of this treatment, the temperature began to rise, attaining normal within four hours, and 100.6° F. within 12 hours. From then on the patient recovered uneventfully with the temperature fluctuating only little above and below normal.

Recapitulation. The statistical analysis outlined above, then, discloses that if the data be accepted as they stand, Type A antiserum approaches a gradient of efficiency of about 50 per cent. Stated in other terms, it appears that the usual survival rate of 20 to 25 per cent has been doubled in the present study. Although less dramatic in its effect than antipneumococcal serum—unquestionably the most effective of the antibacterial sera in cur-

ient use—the indications are that in the ultimate analysis, Type A anti-staphylococcal serum may provide comparable benefits, since both approximately double the usual survival rate of their respective infections. It must be remembered that the pneumococcus, although capable of causing massive infection, rarely destroys tissues or forms abscesses. The tremendous pulmonary involvement incited by this organism is characterized by a filling of the alveolar spaces with exudate which regresses so completely and benignly with recovery that no sign of the past infection remains. Surrounded by an ectoplasmic layer of carbohydrate, moreover, the organism reacts immediately with homologous antiserum, and it is, therefore, rapidly and effectively immobilized. In the case of the staphylococcus, on the other hand, the infection is essentially a process of abscess formation and tissue destruction with healing by cicatrization, and whatever the action between carbohydrate and antibody, it is necessarily delayed because of the endoplasmic distribution of the carbohydrate. It is small wonder, then, that anti-pneumococcal serum should initiate a more dramatic effect than anti-staphylococcal serum.

The recoveries in this series represent different varieties of septicemic infection, as brought out in table 1. The primary focus varied from an infected pimple to the grosser diseases of pneumonia, meningitis or uterine infection resulting from self-induced abortion. The most impressive action of the serum, however, was witnessed in patients with osteomyelitis and septicemia. Thus, 27 such individuals were observed, of these 24 recovered, and three died. Of those recovering, only four have thus far returned for further care, as removal of sequestrum. Of those dying, one had reached the stage of endocarditis before administration of serum, one, pericarditis with a ruptured abscess of the heart muscle causing a direct communication between heart chamber and pericardial sac, and the third patient arrived at the hospital when the supply of serum did not permit adequate treatment. In this third case the blood was sterilized with the serum on hand, but the blood culture became positive again several days later. Because additional serum was not available, the patient received no more specific treatment, although in need of it. The condition became rapidly worse and within a week the patient died. Because of the complications in these three cases, it may be justifiable to attribute death to causes other than failure of serum.

In two other patients of this group, however, it was questionable whether the serum was of great assistance. In one the leg was finally amputated before recovery ensued, and in the other, despite the occurrence of a strong skin reaction to Type A carbohydrate, and precipitins in the blood to a titer of 1:200,000, the blood culture remained positive for several days before sterilization. Unless it is assumed that the antiserum prevented greater extension than was present, it must be admitted that the clinical condition changed very little, if any, during serum therapy. In any case, however, the ratio of survivals to deaths in this group is particularly high. It is felt

that gratifying results here were aided by the early administration of the serum in practically all the cases, and that, therefore, it is reasonable to deduce that if serum is to be given, then the sooner it is used, the greater its effectiveness

SYNOPSIS OF PATIENTS DYING

Upon analysis of those cases in which the infection proved fatal it soon became evident that death in many of the cases was inevitable since there was evidence that the infection had advanced beyond help by any form of treatment. During the past year, for example, the type of patients referred for serum treatment became particularly unfavorable due to prolonged, unsuccessful treatment with sulfonamides beforehand, as has already been brought out in a joint report from this laboratory and the Philadelphia General Hospital.⁶ This resulted not only in the late administration of serum but frequently enough rendered prognosis hopeless. Consequently, if a fair estimate of the value of the serum is to be obtained, it is necessary to give a breakdown of the mortality figure. That a rapid impression may be gained of the factors entering into the death of the patients, certain data have been brought together in the form of protocols. In table 2, therefore, a summary of the fatal infections is given based on portal of entry. Of the 54 patients listed, seven became infected by way of furunculosis and miscellaneous

TABLE II
Summary of Fatal Infections Classified by Initial Infection

Total number of patients treated	102
Total number of patients dying	54
Furunculosis	7
Localized abscesses (miscellaneous)	7
Undetermined	7
Terminal septicemia (see text)	4
Pneumonia *	4
Osteomyelitis (see text)	3
Cellulitis	3
Sinus thrombosis (from infected pimple)	2
Sinus thrombosis (from panophthalmitis)	1
Drug poisoning with abscesses (see text)	2
Infection of foot	2
Draining chronic sinus	2
Postoperative infection (prostatectomy)	1
Otitis media (bilateral)	1
Endometritis (spontaneous abortion)	1
Perinephric abscess	1
Infected scratches (see text)	1
Pemphigus with cellulitis	1
Pneumonia following chickenpox	1
Leukemia with unexplained septicemia	1
Nephrosis with multiple abscesses	1
Infected pimple with pneumonia and endocarditis	1
Total	54

* In addition to the primary pneumonias listed, there were 12 examples of metastatic pulmonary infection

localized abscesses, while in seven others the original focus was not satisfactorily established. Staphylococcal septicemia terminal to some other pre-existing condition (congenital jaundice, twice, malnutrition and congenital heart disease once each) was encountered four times, and in four others the primary lesion was in the form of pneumonia. In the latter connection, it should be pointed out that in addition to the primary pneumonias, there were 12 examples of metastatic pneumonia. Three more cases started by way of osteomyelitis as already discussed above. The remaining 22 patients represent a miscellaneous group, for the most part, of individual examples, as tabulated.

If, now, the fatal infections are reclassified on the basis of various factors entering into and, perhaps, contributing to the serum failures, a number of interesting features are brought to light. This information is summarized in table 3, and lends itself most readily for presentation under the topical order employed therein.

TABLE III
Summary of Miscellaneous Factors Contributing to Serum Failures

Factor Encountered	Number of Patients	% of Total Treated
Patients with endocarditis	15	15
Patients dying within 72 hours	15	15
Death due to other causes	5	5
Serum treatment excessively delayed	4	4
Patients with pericarditis	3	3
Patients with sinus thrombosis	3	3
Miscellaneous	9	9
Total	54	54

Patients with Endocarditis Of the 54 patients dying during serum treatment, 15 (or 15 per cent of the total treated) gave clinical evidence, before serum was started, of endocarditis which was subsequently confirmed at postmortem examination. This condition proved to be invariably fatal. The bacterial count of the circulating blood always ran high (hundreds or thousands of colonies per c c) and did not appear to be influenced by the serum. In order to illustrate the ineffectiveness of Type A antiserum in endocarditis a brief résumé will be given of case 51.

Case 51 A white girl of 13 years entered the hospital after two weeks of high temperature, severe "cold" with general malaise, occasional chills and frequent urination (two and three times an hour). She was treated with sulfapyridine until the twenty-third day when serum was administered, at a time when endocarditis had become clinically evident. The patient received a total of 640 c c of serum intravenously over 11 days without affecting the general condition, the skin test to carbohydrate, or the septicemia which ran from 1200 to 4000 colonies per c c of blood. At postmortem examination there was found a massive vegetation of the tricuspid valve, almost completely obliterating the lumen.

It is the writer's opinion that in staphylococcal endocarditis the prognosis is unfailingly fatal and no method of treatment now exists for alleviating or arresting this condition. It is felt, however, that since *so often* endocarditis is a later development of septicemia, early, adequate treatment may prevent its occurrence in at least a certain proportion of the patients.

Patients Dying Within 72 Hours That a large share of the patients studied were referred when the prognosis was poor is evidenced by the 15 individuals (15 per cent of the total number) who died within 72 hours after starting serum. In fact, two-thirds of this number died within 48 hours. It is readily seen how hopeless the condition was, and in any case, this group cannot be considered as a fair trial for any experimental treatment.

Death Due to Other Causes Five patients of those dying are, curiously enough, examples of successful treatment despite fatal termination. In each individual the septicemia had been eliminated, and the patient was apparently improving when death intervened through a superimposed condition. Thus, in an elderly man, the complication was lobar pneumonia due to pneumococcus, Type VIII; in a child, hemorrhage of the carotid during an operation of the throat caused exsanguination, in a middle-aged man under treatment for syphilis, in whom there was originally arsphenamine poisoning with dermatitis which became the primary site of infection, death was due to arsenic poisoning as autopsy later demonstrated, in the fourth (case 83 above) subsequent invasion of the blood stream by hemolytic streptococci was the final cause of death, in the fifth patient, the original difficulty was a perinephric abscess which was treated surgically by nephrectomy with subsequent infection at the site of operation, the septicemia and local infection subsided but there was a persistent pulmonary infection which after about three months caused death. Up until autopsy, the lung involvement was considered staphylococcal in nature, but this was an erroneous assumption since the process revealed itself as one of actinomycosis, probably even antedating the staphylococcal infection. It is important that staphylococci were not recovered from heart blood cultured at postmortem examination and that the organs and tissues were free of metastatic abscesses.

Serum Treatment Excessively Delayed Further analysis discloses that four patients were started on serum late in the disease. After this study was under way, it was anticipated that a certain proportion of the patients would be treated at a later date than desired. In these four, however, the delay exceeded any anticipations. Thus, serum treatment was started on the twenty-eighth, fifty-first, fifty-second, and fifty-eighth days of illness, respectively. Perhaps the surprise should be not that the serum failed to check the infections, but that the patients lived as long as they did.

Patients with Pericarditis Three other patients had extensive pericarditis when first seen. In two (including the one mentioned above) an abscess in the myocardium had ruptured into the pericardial sac. In both cases leaking blood had clotted and become adherent to the visceral and parietal peri-

rdium Numerous small colonies of staphylococcus were distributed throughout the clot. As with the cases of endocarditis these must be considered as failures on the part of the serum, and, most probably, hopeless complications of staphylococcal infection.

Patients with Sinus Thrombosis There were three instances of this condition, each further aggravated by secondary meningitis. All three patients died, leaving no doubt that the serum had been of no benefit. It seems that as in the case of cardiac infection, sinus thrombosis is beyond help by this serum.

Miscellaneous Patients Dying In three other individuals death was unquestionably due to staphylococcal infection, but in each instance a type of complication had arisen which placed the predominant focus beyond the reach of serum. Thus, in an elderly diabetic (case 20), there had been a thrombophlebitis of the femoral vein extending from the knee to an inch beyond the bifurcation of the vena cava. The circulation had been completely blocked and a huge clot riddled with innumerable colonies of staphylococci extended along the distance described. The second example was an elderly man (case 35) who fell from a ladder, scraping his thigh which was the original focus of infection, and suffering retroperitoneal hemorrhage presumably from the left kidney which was not suspected until autopsy. Apparently the bleeding continued at a reduced rate for some time following the accident, and at autopsy there was a massive blood clot adherent to the left kidney and studded with staphylococcal colonies. The third case was a diabetic of long duration (case 81) whose infection started by way of a boil in the sacral region and eventually reached the prostate gland. At post-mortem examination there was revealed for the first time more or less complete destruction of the prostate with a large pocket of pus in its place that had eroded through the rectum causing open passage (fistula) between this area and the intestinal canal. It is interesting that in the first two patients no metastatic abscesses were located at autopsy, while in the last the only abscesses found were several scattered ones in both kidneys, a surprisingly slight degree of dissemination considering the nature of the case, the infection, and duration of septicemia (ca. two weeks).

In one of two patients with pneumonia (cases 48 and 49) the disease was secondary to influenza, and in the other to a boil on the left shoulder following "home treatment." In both instances the infection at first treated with sulfonamides did not respond to serum given daily over six and eight days respectively.

The last four patients represent miscellaneous conditions. In one (case 44) a young infant with congenital icterus, the septicemia was considered terminal. It did not respond to serum treatment. Case 41 was already suffering with paresis including a dissecting aneurysm of the aorta, and tuberculosis of the spine. The latter caused almost complete destruction of the third lumbar vertebra at which site staphylococci first appeared. He was treated intensively with antistaphylococcal serum without clearing of the

original focus, receiving 280 c c of serum over a period of four days, with sterilization of the blood. He nevertheless died one week following the last injection of serum. Death in the third patient, a young male adult (case 19) was described by the physician in charge as due to a "gross diagnostic error." A diagnosis of meningitis and septicemia had been made, and serum was given intravenously and intrathecally; the blood culture became sterile, meningeal symptoms disappeared and the patient was apparently improving when death came unexpectedly. At autopsy a large paravertebral abscess was found. It was so close to the surface that drainage would have been a simple matter with possibly a different outcome. Postmortem examination disclosed no metastatic abscesses in the organs and tissues. The final patient is the one referred to previously who entered the hospital with osteomyelitis and septicemia at a time when the supply of serum was particularly low.

Analysis of Postmortem Observations Of the 54 patients dying, autopsies were performed on 37, it being impossible to obtain the necessary permission in the remaining 17. Study of the 37 bodies revealed that extensive metastatic abscesses were demonstrable in 21, while in two the number of metastatic abscesses appeared to be less than had been anticipated. In 11 of the remaining 14 no metastases were found, in three, however, there were hemorrhagic infarcts in different organs. The indications are, therefore, that with due consideration of the early deaths, the patients with endocarditis, and the delayed serum treatment in the instances cited, the proportion of cases appears high in which visceral dissemination was not observed. In any case, the rate as it stands is about 30 per cent.

In rapid fulminating infection terminating fatally, it is possible that no metastatic abscesses may occur, since abscess formation requires a certain interval of time. Since the cases reported here were for the most part prolonged infections, it seems not unlikely that prompt administration of serum may reduce the spread of infection to the different organs and tissues.

RECAPITULATION

That the data derived from this study might be examined at a glance, the final results of serum treatment have been appended in table 4 in the form of a classification by chief clinical symptoms. As stated above, osteomyelitis was the most frequent forerunner of septicemia and responded best to serum with a survival of 24 out of 27 patients. Endocarditis occurred next in frequency in 15 patients. This condition was completely refractory to Type A serum and was characterized by uniform fatality. Of 14 patients with furunculosis and varying metastatic infection, seven survived and seven died. Primary pneumonia contributed eight patients with four deaths and four survivals. In this connection may be mentioned 22 patients with pneumonia secondary to a primary surface lesion, 12 died and 10 survived. Four patients each with cellulitis with metastases, and septicemia terminal to

some other condition, were treated with antiserum and all died. Pericarditis and sinus thrombosis with secondary meningitis occurred in three patients each, and was fatal in every instance. Primary meningitis seen three times, and endometritis following abortion seen twice ended with recovery in each case. The remainder forms a group of 19 patients with a variety of conditions representing for the most part individual examples. The end result in this group showed eight recoveries and 11 deaths. It may be of interest to add that staphylococcal septicemia was encountered in diabetes on five occasions. Although they all died, it is felt that there were other factors involved, so that the combination of diseases need not necessarily imply a fatal termination.

TABLE IV
Final Results of Serum Treatment, Classified by Predominant Clinical Symptoms

Chief Clinical Manifestation	Number of Patients				% Recovery
	Treated	With Septicemia	Survived	Died	
Osteomyelitis	27	26	24	3	89
Endocarditis	15	15	0	15	0
Furunculosis with metastases	14	14	7	7	50
Pneumonia	8	5	4	4	50
Cellulitis with metastases	4	4	0	4	0
Terminal septicemia	4	4	0	4	0
Pericarditis	3	3	0	3	0
Sinus thrombosis	3	3	0	3	0
Endometritis following abortion	2	2	2	0	100
Meningitis	3	3	3	0	100
Miscellaneous	19	19	8	11	45
Total	102	98	48	54	47 (average)

That the therapeutic results are perhaps dependent upon the activity of the serum rather than some personal factor of management may be seen in a comparison of the statistics collected in different areas. Examination of the data assembled in table 5 illustrates the results obtained from St. Louis and vicinity by the writer, from the Philadelphia General Hospital, and from scattered cities throughout the country to which serum has been sent on request. Thus, in St. Louis, 62 patients were treated with a recovery rate of 45 per cent, in Philadelphia, there were 22 patients with the same rate, and the scattered cases represent 18 individuals and a therapeutic efficiency of 55 per cent. The 10 per cent difference among the three was probably influenced by the fact that all but two cases of endocarditis and all of the cases of sinus thrombosis and pericarditis occurred in the St. Louis and Philadelphia groups.

If the running summary supplied above on the fatal infections actually depicts what have been considered as unusual conditions of study, it is possible that Type A antiserum has greater therapeutic value than has been demonstrated. The large number, alone, of hopeless patients accepted for

treatment (15 dying early, four treated excessively late, together with the 18 presenting cardiac infection) accounts for better than two-thirds of all the deaths. However, until statistical evidence of sufficient magnitude becomes available from different sources, the therapeutic potentiality and appraisal of Type A antiserum must remain in abeyance. In the meantime, no amount of explanation and theorization can affect the final outcome.

TABLE V
Comparison of Therapeutic Effectiveness of Type A Antiserum in Different Areas

Locality	Number of Patients			% Recovery
	Treated	Survived	Died	
St. Louis	62	28	34	45
Philadelphia	22	10	12	45
Scattered	18	10	8	55 *
Total	102	48	54	47

* Oddly enough, only two cases of cardiac involvement are included in this group which may help to explain the higher percentage.

DISCUSSION

Since pathogenic staphylococci are phagocytized by so-called normal cells, it is necessary in any discussion concerning treatment to include the possibility of nonspecific activity. Obviously, if a therapeutic agent stimulates leukocytosis, for example, then the degree of phagocytosis taking place may well be proportionately enhanced. With increase in phagocytosis, one may logically assume synchronous promotion of bacterial immobilization and finally disintegration. To this extent, then, any treatment incorporating foreign proteins, toxic split products, etc., might conceivably be of benefit, and in certain instances of not so severe infection, it might afford the assistance required for recovery. In more or less critical disease bacterial elimination imposes greater demands on the treatment which may explain the limited success of some of the agents introduced in the past (e.g., foreign proteins, toxic metals, antiviral of Besredka, bacteriophage, and even antitoxin in which, however, there is a degree of specificity as well). That Type A antiserum possesses a distinct specific element is indicated by the observations in case 83 described above, and by certain experiments still under study on the antibody analysis of this serum. It seems to the writer that although Type A antiserum undoubtedly possesses nonspecific properties, its additional value resides in its specific (i.e., anticarbohydrate) constituent.

The data already reviewed suggest that Type A antiserum may have a certain value in the treatment of staphylococcal septicemia accompanying a variety of clinical manifestations. While the current rate of survival has been close to 50 per cent, it is felt that with better application of the principles of serum therapy and better understanding of the nature of staphylococcal

infection, this proportion may possibly be raised in the future. Thus, if serum is administered as soon as indicated, if surgical drainage is instituted as soon as feasible, and if the supportive care suggested at the time is supplied, then the antiserum would be given optimum conditions for testing its therapeutic capacity. It must be remembered that prolonged staphylococcal septicemia invariably leads to widespread abscess formation, and as the abscesses become numerous, the prognosis becomes grave, first, because the abscesses intensify the septicemia by discharging into the circulation, and second, because the abscesses are more frequently than not surgically inaccessible. The logical treatment, therefore, should be directed toward elimination of septicemia and prevention of metastatic infection. That Type A serum may actually accomplish this end, in certain cases, at least, is exemplified by the patients who survived and those who reached the autopsy table without metastatic foci despite extended septicemia.

It is desirable to emphasize again the importance of surgical drainage. Evidence reviewed above indicates the inability of the antiserum to control localized lesions. It is necessary, therefore, to evacuate abscesses by artificial methods. This aids not only the elimination of innumerable staphylococci but allows the escape of the toxic substances formed by the bacteria and by tissue destruction.

SUMMARY AND CONCLUSIONS

1 Ninety-eight patients with staphylococcal septicemia and four with severe infection without septicemia have been treated with specific Type A antibacterial serum prepared in rabbits.

2 All the staphylococci isolated in this study fermented mannite and contained Type A carbohydrate. None of the strains was particularly virulent for white mice. About half of the strains were tested in rabbits, and a lesser number in guinea pigs, their virulence for these animals also was considered low.

3 In addition to the antiserum, treatment included surgical drainage and supportive care.

4 Of the patients treated, 48 survived and 54 died, in the latter group there were five patients who, although dying of other causes, recovered from the staphylococcal septicemia.

5 Type A antiserum exerted its greatest effect in osteomyelitis present with septicemia, 26 patients were treated, and 23 recovered, three died as explained above. An additional patient with bacteremia recovered.

6 The least promising results were observed in cardiac infection and sinus thrombosis, there were 18 patients in the former group and three in the latter, all of whom died.

7 Of the 54 patients dying, 15 succumbed within 72 hours after starting serum, this and other conditions tabulated in the text suggest that all the

failures may not have been entirely due to impotency on the part of the antiserum.

8 The data indicate at this time a twofold increase in the usual survival rate, but actual evaluation of the serum will have to await future work from different sources

ADDENDUM

Since this article went to press, six additional patients have been treated with Type A serum according to the procedure described in this paper. Four of these patients survived and two died. Those recovering were all examples of septicemia secondary to (1) apparently sinus thrombosis, (2) osteomyelitis, (3) pneumonia, and (4) furunculosis. Those dying were patients with septicemia and (1) endocarditis, (2) brain abscesses.

Note It is not practical at this time to thank the numerous physicians, surgeons, and nurses who have contributed so graciously to this study. Special acknowledgment, however, must be made to Drs. Alexis F. Hartmann and David P. Barr of St. Louis, Drs. Harry G. McNamee and the late Robert G. Torrey of Philadelphia, and the Lederle Laboratories and the Eli Lilly Co.

REFERENCES

- 1 JULIANELLE, L. A. Observations on the specific treatment (Type A antiserum) of staphylococcal septicemia, *ANN INT MED*, 1939, xiii, 308-316
- 2 JULIANELLE, L. A., and WIEGHARD, C. W. The immunological specificity of staphylococci. I The occurrence of serological types, *Jr Exper Med*, 1935, lxii, 11-21. II The chemical nature of the soluble specific substances, *ibid*, lxii, 22-30
- 3 JULIANELLE, L. A., and HARTMANN, A. F. The immunological specificity of staphylococci. IV Cutaneous reactions to the type specific carbohydrates, *ibid*, 1936, lxiv, 149-159
- 4 JULIANELLE, L. A. Determination of staphylococcal types by fermentation of mannite, *Proc Soc Exper Biol and Med*, 1937, xxxvi, 117-119
- 5 McNAMEE, H. G. The treatment of severe staphylococcal infection with specific Type A antibacterial serum, *Ann Surg*, 1942, cv, 308-317
- 6 TORREY, R. G., JULIANELLE, L. A., and McNAMEE, H. G. The sulfonamide therapy of staphylococcal septicemia, *ANN INT MED*, 1941, xv, 431-445

WILLIAM WITHERING: HIS CONTRIBUTION TO MEDICINE¹

By JONATHAN C MEAKINS, F A C P, *Montreal, Quebec, Canada*

ON March 17 of the year 1741, two hundred years ago, there was born at Wellington, in Shropshire, to Edmund Withering and his wife, Sarah Hector, a son who was to be known as William. The event was not heralded by any celestial phenomena or terrestrial disturbances.

Our scene really opens in the latter half of the century, a period of intellectual, scientific and political unrest and consequent progress. The seeds of independence and freedom of man were in the state of germination. The writings of Rousseau and Hume were influencing men's political outlook. The American revolution against traditional privilege or so-called tyranny was in the offing in spite of the Pitts, father and son, and of Charles James Fox, the cloud as small as a man's hand foretelling the bloody French revolution was barely visible on the political horizon, and Frederick the Great was seeking to weld a new Teutonic order in Europe.

In more peaceful mold Watt was developing the steam engine, Murdock invented gas-lighting, and Davey was soon to perfect his lamp. Black and Priestley were making notable advances in chemistry, the Munroes, Cullen and Hunter, were outstanding figures in Medicine, and Adam Smith was laying the basis for our present science of economics.

It was in this environment of teachers and companions that William Withering entered his professional life and training in Stafford and later Birmingham. The therapeutic era of bleeding, emesis, purgation and clysters was drawing to a close—although it knew it not—to be replaced by the little less tragic period of polypharmacy.

The record of William Withering's career at Edinburgh does not reveal any outstanding feats of academic excellence. He apparently took advantage of all the University could give in the way of education, social contacts and student activities. He undoubtedly spent his time and money to good purpose and returned to practice his profession in the small town of Stafford not far from his birthplace, in the Marches of Wales. The choice of this place as against the region where his family had been well known as physicians for generations reveals an independence of action which up to this time would not have been expected. He seems to have been possessed of all the virtues and few if any of the vices of the young men of his day. Wine, women and song do not appear to have entered into his life, even when on the traditional "grand tour" of the Continent, if one is to believe the whole tale as told in letters and the character of his companions. I may do him an injustice, but I am afraid not!

* Read at the Boston meeting of the American College of Physicians April 22, 1941

Apparently it was in 1767, his twenty-seventh year, that Withering began to practice. I cannot help but believe that he was one of those whose intellectual growth comes relatively late and is forced into bloom by extraneous influences comparable today to the use of ultraviolet light in henneries or a shot of vitamin B complex to plants and flowers. He had, up to this time, been interested in geology, mineralogy and antiquarian matters which were all of a highly respectable character. The science of botany had experienced a slight rejuvenation during the Renaissance but, in a medical sense, had remained in the hands of the apothecaries, herbalists, "old women," and many others whom we would today class as "irregular practitioners" in our most disdainful manner. It is true that the publication of "*Flora Lappoinca*" by Linnaeus (1737) gave an indication of the future, and later in the same year the appearance of his "*Genera Plantarum*" and in 1738 his "*Classes Plantarum*" initiated modern systematic botany. Natural history was experiencing a fashionable boom at this time, so it was but natural that Withering should join in the tide, as he did in the other social activities of the time, such as lawn bowling, amateur dramatics, and musicales, he even played the flute and Scottish bagpipes—a hang-over from his student days in Edinburgh. It would seem that a more primitive urge than either science or society led him to the pursuit of botany.

One of his first patients was Miss Helena Cooke to whom he would appear to have had a softer attachment than that engendered by a lucrative patient. Miss Cooke was also a young lady of the period, as she indulged in flower painting. It is not clear whether this was after the manner of occupational therapy or a really social urge. However that may be, Withering on the meagre rounds of his practice, or perhaps during lovesick strollings through the meadows, collected and brought to her flowers and plants as models for her artistic endeavors. So began his interest in botany which eventually culminated in his publication in 1776 of "*A Botanical Arrangement of All the Vegetables Growing in Great Britain with Descriptions of the Genera and Species According to Linnaeus*". A most portentous title as is proper for such a subject! There was little that was original about this volume unless it were that it was written in English and was apparently considered to be a complete account of these bucolic plants, actually much of it was really a translation from the Latin of other texts. There were included 12 copper plates which apparently were not after the paintings by his wife, if they had been, it would have been a delicate touch of collaboration. Although this book was a best seller, Withering's original work lay more in chemistry and geology. He was specially interested in the composition of the water of the medicinal springs and spas of Great Britain, and in mineralogy was the discoverer of native barium chloride which was later named "Witherite" in his honor.

It would seem apparent that his interest in medicinal waters was the first indication that his thoughts were being directed to therapeutics. In the

medical writings of the period dropsy was as baffling a problem as its synonym "edema" is today. It was, therefore, quite logical that the gossip of a supposed cure by some herbal concoction should have intrigued a botanist and a therapist. It is a well known tale of how Withering was asked his opinion of a family (and supposedly secret) remedy for dropsy, known to an old woman of Shropshire, his home county. This concoction contained some 20 or more ingredients. Of these Withering states "It was not very difficult for one conversant in these subjects to perceive that the active herb could be no other than foxglove." This statement would strongly suggest that the foxglove had a local reputation at least in domestic medicine even if it had not reached the dignity of being included in the official pharmacopoeia of the time. It is not really surprising that this should have been so. In fact, Withering did not discover digitalis as much as the foxglove discovered Withering. It was a common weed of the countryside with a virtuous reputation of good works in Shropshire, Warwickshire and Yorkshire, and probably elsewhere, which needed a discrete press agent rather than a discoverer. That Withering fulfilled this part is much to his credit. One has only to read the account of some of his cases of which the following is a good example, to appreciate what a boon this drug was then as it is today.

CASE XCIV

"July 5th Mr C , of W , Aet 28 Had drank very freely both of ale and spirits, and in consequence had an ascites, very large legs, and great fulness about the stomach. He was ordered to take the Infusion of Digitalis night and morning for a few days, and then to keep his bowels open with chrystals of tartar. The first half pint of infusion relieved him greatly, *after* an interval of a *fortnight* it was repeated, and he got well without any other medicine, only continuing the chrystals of tartar occasionally. I forgot to mention that this gentleman, before I saw him, had been for two months under the care of a very celebrated physician, by whose direction he had taken mercurials, bitters, squills, alkaline salts, and other things, but without much advantage."

It should here be stressed that popular belief attributed the virtue of digitalis to the vomiting and purgation which it induced. Withering knew better than this and rightly sought to induce diuresis without the toxic symptoms almost constantly induced by massive doses, as recounted in the following case.

CASE CVI

"November 2d Mr S , of B h , Aet 61 Hydrothorax and swelled legs. Squills were given for a week in very full doses, and other modes of relief attempted, but his breathing became so bad, his countenance so livid, his pulse so feeble, and his extremities so cold, that I was apprehensive upon my second visit that he had not twenty-four hours to live. In this situation I gave him the Infusion of Digitalis stronger than usual, viz two drams to eight ounces. Finding himself relieved by this, he continued to take it, contrary to the directions given, after the diuretic effects had appeared.

"The sickness which followed was truly alarming, it continued at intervals for many days, his pulse sunk down to forty in a minute, every object appeared green to his eyes, and between the exertions of reaching he lay in a state approaching to syncope. The strongest cordials, volatiles, and repeated blisters barely supported him. At length, however, he did begin to emerge out of the extreme danger into which his folly had plunged him, and by generous living and tonics, in about two months he came to enjoy a perfect state of health."

Withering knew well the symptoms and signs of digitalis intoxication. It was his constant endeavor to combat the folly of the laity and the profession in the use of the drug. Furthermore, he acknowledged his ignorance of the proper dosage and was constantly striving to devise a safe method of standardization which was not accomplished until a century and a quarter had passed. He appreciated that the drug varied in concentration in different plants, in different parts of the same plant, and at different times of the season, and finally he determined that different manners of preparation were of greatly varied potency. He eventually advised that the leaves should be gathered just before blossoming time, the midrib removed, and the leaf blade alone dried in the sun or before a fire. They were then ground to a fine powder and the dose for an adult was one to three grains of this powder twice a day. How modern this sounds!

Many have praised William Withering for the introduction of foxglove into our therapeutic armamentarium. This does not impress me nearly as much as the fact that he *kept* it there. He knew full well that the vomiting, diarrhea, bradycardia, cardiac arrhythmias, visual disturbances, sudden death, etc., were due to excessive amounts of the drug.

CASE CVII

"November 19th Master S, Aet 8 Ascites and anasarca. A dram of Fol Digitalis in a six ounce infusion, given in doses of a spoonful, effected a perfect cure, without producing nausea."

He continued to emphasize that diuresis was the optimum objective. Even though he attributed this to a direct action on the kidneys and did not consider its cardiac effect, this in no way detracts from his contribution to Medicine. He was conscious, however, that it had an influence on cardiac function since in the ninth and last of his inferences he states "that it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends." This statement was probably based upon shrewd observations of the pulse, as revealed by the following excerpts from his records:

Case II—before treatment "her pulse was extremely weak and irregular" after digitalis "her pulse became more full and regular"

Case XX—"sudden violent palpitation of his heart"—infusion as before which very soon removed his complaints

Case XXXI—"her pulse very small and slow" digitalis had been given by a colleague who had seen Withering prescribe it before, but he had not "attended to

stop the exhibition of the medicine when its effects began to take place. The great distress of her situation was evidently owing to the imprudent and unlimited use of Digitalis. The third day the pulse was not so slow."

Case LXXVIII—"it lowered his pulse"

Case CVI—already mentioned

Case CXVII—"at length I was urged to give the Digitalis, and considering the case as desperate, I agreed to do it. The event was as I expected, no increase in the urine took place, and the medicine being continued, his pulse became slow, and he apparently sunk under its sedative effect. He was neither purged nor vomited, and had the Digitalis been omitted altogether or suspended upon its first effects upon the pulse being observed, he might perhaps have existed a week longer."

Case CXXI—"Pulse 132. I mention this case to point out the great effect the Digitalis has upon the heart, for the pulse came down to 96 and the pulse never became quicker."

Case CXXIX—"The intermitting pulse. He recovered his usual health."

Case XXXII—"pulse 160 tremulous beats in a minute, but the pulsation in the carotid arteries was such as to be visible to the eye, and to shake his head so that he could not hold it still." The diagnosis seems in little doubt but there is no further mention of the pulse.

Case CLXII—"his pulse very small and quick"—no further mention.

Mr Causer's 1st case—"an irregular pulse"—no further mention.

Mr Causer's 2nd case—"a very irregular, intermittent pulse." "Pulse better."

Dr Stokes' 1st case—"Pulse irregular, with frequent intermissions"—no further mention.

Dr Stokes' 3rd case—"Pulse intermitting"—no further mention.

Mr Young's 1st case—"the pulse small and quicker than usual"—no further mention.

Mr Young's 2nd case—"the pulse varying between 94 and 100 and feeble—no further mention."

Mr Young's 3rd case—"his pulse feeble and intermitting" after it is stated "The pulse in a few hours became regular, slower and stronger."

Mr Young's 5th case—"The pulse exceedingly strong and rebounding beating 114 to 120 every minute"—Corrigan—neither digitalis nor "Repeated bleeding had any effect in diminishing the violent action of the heart."

Mr Young's 8th case—"Pulse feeble"—no further mention.

From some 212 cases of his own and those reported to him by his colleagues the pulse is mentioned only 19 times, but it is only in nine cases, seven of which were reported by Withering and one by Young, that any after effect upon the pulse is noted, and in seven it is stated that it became slower. This is not much evidence upon which to base his ninth inference, but it was more than anyone else had noted at the time and not much less than was known a hundred years later when Mackenzie published his epochal work.

Withering used the drug for many conditions which would seem to have included congestive failure, nephritis, cirrhosis of the liver, tuberculous peritonitis, pulmonary tuberculosis, ovarian cyst, etc. There is no doubt that he had a shrewd idea that it was much more efficacious in some of these than in others, but at no time does he definitely commit himself. This may have been due to his native modesty, although I should doubt it. He was not given "to hiding his light under a bushel," but rather to an appreciation of his superior knowledge—which is always an asset in this life.

It was in 1775 that he started to use this drug. In 1783 digitalis was included in the Edinburgh Pharmacopoeia, which was two years before the publication of his "Account of the Foxglove." This book was not published to introduce digitalis but to preserve it, as Withering definitely states in the following words:

The use of the Foxglove is getting abroad and it is better the world should derive some information, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable.

His published notes on cases constantly reiterate caution and point out the drug's dangers and virtues in a manner that could not be surpassed by any other means. As he said "Poisons in small doses are the best medicines, and the best medicines in too large doses are poisonous." But have we taken advantage of this great contribution to our therapeutics? I hazard to answer this question in the negative. I am sure William Withering would turn in his grave if he knew that today, 142 years after his death, digitalis poisoning is the most common intoxication encountered in the medical wards of a general hospital.

If William Withering were given to profanity, which I greatly doubt, I can hear him cry "God's blood! How can they be so damned foolish after all my admonitions!"

CASE REPORTS

ACUTE HEMOLYTIC ANEMIA CAUSED BY SULFATHIAZOLE *

By JOSEPH J. BUNIM, M.D., *Brooklyn, N. Y.*, and MURRAY ISRAEL, M.D.,
Williston Park, L. I., N. Y.

THE first case of hemolytic anemia resulting from sulfanilamide was reported by Harvey and Janeway¹ two and a half years after Domagk had introduced this drug into clinical medicine in 1935. Since then a number of similar reports have appeared, and W. B. Wood² found the incidence of this toxic reaction to be as high as 40 per cent in his series of 522 cases at the Johns Hopkins Hospital. Two fatal cases^{3,4} have already been described. The sulfapyridine derivative, introduced by Whitby in 1938 primarily as an effective chemotherapeutic agent against the pneumococcus, offered, in addition, the not unimportant advantage of provoking less serious toxic reactions insofar as the hemopoietic system was concerned. The number of reported cases of hemolytic anemia resulting from sulfapyridine has been very few, though recently Ravid and Chesner⁵ have reported the first fatal case. Sulfathiazole, first described by Fosbinder and Walter⁶ and by Lott and Bergeim⁷ in 1939, has been found to be as effective as sulfapyridine in the treatment of pneumococcus pneumonia in man and possibly more effective in staphylococcus infections.⁸ Spink and Hansen⁹ report that "there is no doubt that sulfathiazole is more effective than sulfapyridine in the treatment of staphylococcal septicemia and appears to be the best therapeutic agent available for this infection at the present time." The low toxicity of this substance in the experimental animal and in man has been emphasized by several workers^{10,11,12}. In the series of 100 patients treated with sulfathiazole by Flippin, Schwartz and Rose¹² and among the 128 patients treated by Spink and Hansen,⁹ hemolytic anemia did not occur once. Because of its therapeutic superiority over sulfapyridine in certain infections and because of its comparatively low toxicity, sulfathiazole is used as widely as sulfanilamide or sulfapyridine. The various toxic reactions that may result from this drug should, therefore, be known. It is primarily for this reason that we wish to report a case of severe hemolytic anemia resulting from sulfathiazole.

CASE REPORT

A white male of 38 was admitted to Beth Israel Hospital, N. Y., on September 11, 1940 in the private service of one of us. He had been ill since September 3 and under the care of a local physician until he was admitted to the hospital. His illness began with a cellulitis of the dorsum of the left foot resulting from a secondarily infected toe originally the site of dermatophytosis. Four grams of sulfathiazole were given on the first day, 30 grams on the second, 20 grams on the third and 10 gram each day for the next three days. This chemotherapy was supplemented by ultra-violet radiation to the foot from the second to the seventh day of illness. A 110 volt mercury arc

* Received for publication October 25, 1940

lamp was used at a distance of 8 inches, at first for 10 minutes and then for 25 minutes three times a day. During the first few days of sulfathiazole medication the patient's temperature returned to normal but he complained of an "acute binding sensation" in the lower abdomen which had a girdle-like distribution and was vise-like in character. On the sixth day of illness the cellulitis spread from the dorsum of the foot to the lower two-thirds of the leg and the temperature rose abruptly to 105.5° F. The patient had a severe shaking chill and again became acutely ill.

At this point the question of sulfathiazole toxicity was carefully considered. A blood count showed 4,300,000 red blood cells, 86 per cent hemoglobin, 7,500 white blood cells of which 72 per cent were segmented polymorphonuclears, 10 per cent non-segmented neutrophils and 18 per cent lymphocytes. The urine showed no abnormal changes. Because the cellulitis had spread and was associated with a rise in fever, because the blood picture showed no unusual changes and the patient was not jaundiced, and finally, because only 12 grams of sulfathiazole were given in six days, it was decided to increase the dosage to a little more than five grams the next day. This was administered on the seventh day. Twenty-four hours later the patient became much worse, though his cellulitis was subsiding. He now complained of a dull, unlocalized pain "fleeting from head to foot like a ghost" but centering mainly in the abdomen. He also, on questioning, said he had some tinnitus and impaired hearing. He vomited three times, had complete anorexia and severe thirst. He was prostrated, quite despondent and markedly dehydrated. The patient was moderately dyspneic, his temperature was 102° F and the sclerae had become definitely icteric. The urine, which was dark brown, "prune juice" in color the day before, was now "port wine" in color. A blood count showed 16,150 white blood cells and a stained smear exhibited numerous immature cells, including normoblasts and many toxic neutrophils. Sulfathiazole was discontinued. At this point, on the ninth day of his illness, the patient was removed to the hospital.

TABLE I
Hematological Data *

Day of Illness	1	6	8	9†	10	11	12	13	14†	15	16	18	23
Red blood cells (in millions)		4.30		3.69	2.78	2.84	2.10	3.19	2.95	2.54	2.46	2.35	2.29
Hemoglobin (per cent)		86	83	88	74	67	50	52	52	58	60	55	52
Normoblasts (per 100 w b c)				5	0	0	0	0	2	$\frac{1}{2}$	0	1	0
Reticulocytes (per cent)				0.8		0.5	1.5		5.2	5.0	4.2	3.4	1.6
Platelets (in thousands)				180		150				570			
Plasma cells (per 100 w b c)				0	0	1	1	1	2	0	0	0	0
White blood cells (in thousands)	10.3	7.5	16.1	17.5	15.0	22.0	27.6	33.5	29.6	25.5	24.2	14.6	13.4
Myelocytes (per cent)				0	0	0	5	0	6	5	1	1	0
Polymorphonuclears (non-segmented)	12	10	12	9	10	7	5	0	9	8	8	4	3
Polymorphonuclears (segmented)	71	72	75	75	68	73	64	58	55	54	55	63	69
Lymphocytes				11	11	8	14	33	21	27	29	16	22
Monocytes				3	2	7	9	8	5	3	3	4	2

* We are indebted to Dr. H. Maxwell Burry who furnished us with the laboratory data collected prior to the patient's admission to the hospital.

† On the ninth day there was 1 megaloblast per 200 white blood cells. On the fourteenth day there were 1 megaloblast and 1 myeloblast per 100 white blood cells.

The blood studies are recorded in detail in table 1. For the first few days after hospitalization the neutrophils showed marked toxic changes, the cytoplasm contained toxic granules and the nuclei showed an unusual degree of edema. In many granulocytes the segmented nuclei were disconnected and took a solid, homogeneous, purplish-blue stain, resembling in appearance the nuclei of normoblasts. The red cells showed basophilic stippling and anisocytosis. A search for spheroid erythrocytes revealed none. The fragility test, clotting and bleeding times were normal. On the first and subsequent five hospital days the blood plasma contained free hemoglobin and methemoglobin on spectroscopic examination. The serum bilirubin, determined after removal of the hemoglobin, was 3.1 mg per cent. The non-protein nitrogen was 67 mg per cent. Sulfathiazole determinations on blood, urine and stool are recorded in table 2. The blood culture was sterile.

TABLE II
Sulfathiazole Determinations

Specimen	Day of Illness	Free Sulfathiazole	Total Sulfathiazole
Blood	9	4.0 mg per cent	5.0 mg per cent
Urine	9	28.6 mg per cent	44.4 mg per cent
Feces	9	100 mg per gm	160 mg per gm
Blood	11	0.6 mg per cent	0.8 mg per cent

Although the blood count on admission showed 3,690,000 red blood cells and 88 per cent hemoglobin, the patient was given a transfusion of 500 cc of whole citrated blood within an hour after admission. Another transfusion was given on the second hospital day and a third on the fifth day. Infusions of saline and 5 per cent glucose were given daily for the first four days, in an attempt to accelerate the rate of excretion of sulfathiazole. The urine output (2,250 cc) was about 50 per cent of the fluid intake on the first hospital day but gradually increased until it equaled the intake on the fourth day and thereafter. On the fifth hospital day the hemoglobin disappeared from the blood plasma and urine, the jaundice faded considerably and the patient felt markedly improved. As will be seen in figure 1, the peak in the reticulocyte and leukocyte rise was not reached until five and six days after the hemolytic crisis.

A second non-protein nitrogen determination of the blood done on the eighth hospital day showed a rise to 100 mg per cent. Urinalysis of a casual specimen showed a specific gravity of 1.008, a trace of protein, a positive benzidine test and two to three red blood cells per high power field. The urea clearance was only 25 per cent of normal at a rate of urine flow above 2 cc per minute. No oliguria, anuria or hypertension developed at any time. Cholesterol determinations of the plasma on the thirteenth hospital day showed 167 mg per cent of total cholesterol and 78 mg per cent of cholesterol ester. A bromsulphalein excretion test showed a retention of only 10 per cent at the end of 30 minutes and complete disappearance of the dye from the serum by 60 minutes.

During the second week 12 grams of ferrous sulphate were given daily and later 15 units of liver extract were given intramuscularly for four successive days but no immediate rise was noted in the red blood cell count or the hemoglobin content.

The patient was discharged much improved on September 24, after remaining in the hospital for 14 days. He returned to work on October 14. A blood count done at this time showed 3,300,000 red blood cells and 68 per cent hemoglobin. The blood non-protein nitrogen was 38 mg per cent.

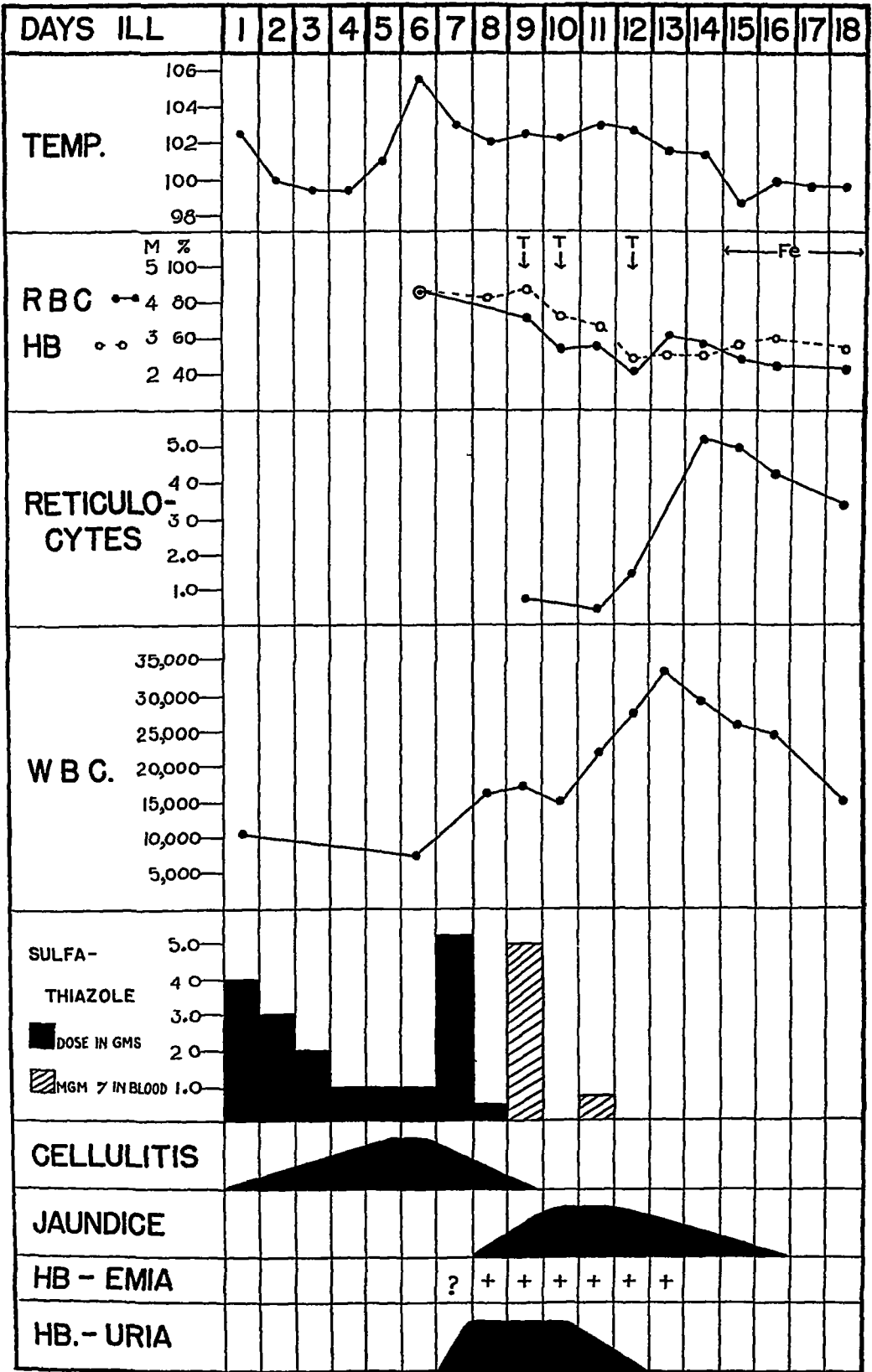


FIG 1 The first eighteen days of the patient's illness He was admitted to the hospital on the ninth day Temp = temperature (rectal), R B C = red blood cells in millions per cu mm, Hb = hemoglobin (Sahl) expressed in per cent, W B C = white blood cells per cu mm, Hb-emia = hemoglobinemia, Hb-uria = hemoglobinuria, T = transfusion, Fe = ferrous sulphate



FIG 2 Film of the peripheral blood on the fourteenth day of illness. A megaloblast is seen flanked on the left by a lymphocyte and on the right by a segmented neutrophile. This preparation showed one megaloblast per hundred white blood cells.

COMMENT

This patient was exposed to ultra-violet radiation for relatively long intervals while he was getting sulfathiazole. Ottenberg and Fox¹³ have shown that when dilute solutions of sulfanilamide are exposed for brief periods to ultra-violet light a strong violet color develops. The nature of this chemical change was not described. We exposed sulfathiazole solutions of varying strengths to ultra-violet light and obtained no such color change. A pale, clear yellow color finally developed. Fox, Hogg and Ottenberg¹⁴ had similar results. They believe that some of the sulfathiazole in the solution is changed upon radiation and that when hemoglobin is later exposed to this irradiated solution it is oxidized to methemoglobin. It is known that patients, when exposed to ultra-violet light while receiving either sulfanilamide or sulfapyridine, may develop severe dermatitis and mucous membrane lesions. However, we have encountered no report of such patients developing hemolytic anemia. Contrariwise, so far as we are aware none of the patients in the reported cases of hemolytic anemia resulting from chemotherapy had been exposed to ultra-violet light. How much the combination of sulfathiazole and ultra-violet radiation contributed towards the development of hemolytic anemia in our patient is difficult to say. It is noteworthy that he developed no dermatitis or mucous membrane lesions and that his course closely resembled that of other patients with hemolytic anemia who had not received any radiation.

The slow excretion of sulfathiazole from the blood, the elevated nonprotein nitrogen and the markedly lowered urea clearance indicate that considerable impairment in renal function had taken place. This may have resulted either from the hemoglobinemia and hemoglobinuria,¹⁵ or from the direct action of the drug on the renal parenchyma, or from both. The liver, on the other hand, seemed to have escaped any detectable damage. The ratio of cholesterol ester

to total cholesterol was well within normal limits as was also the interval in which the liver removed 90 per cent of bromsulphalein from the circulation

SUMMARY

A case of severe acute hemolytic anemia following the administration of 18 grams of sulfathiazole over a period of eight days is reported. The patient developed jaundice, hemoglobinemia, hemoglobinuria, azotemia and impaired renal function, besides the typical blood changes associated with a hemolytic crisis. Following prompt withdrawal of the drug and the institution of the generally accepted form of therapy, the patient recovered.

Addendum Since this paper was submitted for publication, one of us (J J B) encountered a second case of hemolytic anemia resulting from sulfathiazole. The patient was a 52 year old Greek male admitted to the Tuberculosis Service of Bellevue Hospital on March 20, 1941 complaining of fever, chills, cough and pain in the left anterior chest. He had had pulmonary tuberculosis of the right lower lobe for the past five years and had been receiving monthly refills of pneumothorax on that side. During this same period he was also known to have diabetes mellitus and was taking 22 units of protamine zinc insulin daily.

On admission he was found to have pneumococcus type III lobar pneumonia of the left lower lobe. He was also in moderately severe diabetic ketosis. He was treated for the latter condition with the necessary amounts of insulin and intravenous glucose and saline and his urine became free of glucose and acetone in 48 hours. His pneumonia was treated with sulfathiazole. Eight grams of the drug were given on March 21, six grams on March 22 and two grams on March 23, a total of 16 grams. On March 24 it was noted that he was markedly pale, his pulse rate was 120 and his temperature was 101.0° F. There was an icteric tint to his sclera. In 48 hours his red blood cell count fell from 4,100,000 to 2,100,000 and his hemoglobin from 12.0 gm to 9.0 gm per cent. The urine showed an abnormally high content of urobilin without bile. The icteric index of his blood was 17. On March 26 the differential count of his white blood cells showed 30 per cent polymorphonuclears, 29 per cent unsegmented granulocytes, 2 per cent metamyelocytes, 1.5 per cent eosinophiles, 0.5 per cent basophiles, 18 per cent lymphocytes and 19 per cent monocytes.

Two transfusions of whole blood totalling 700 c.c. were given on March 25 and March 26. The patient recovered from this hemolytic anemia as well as from his pneumonia and diabetic ketosis. On April 4 his red blood cell count was 3,800,000, hemoglobin 11.0 gm per cent, icteric index 9 and his general condition was very good.

BIBLIOGRAPHY

- 1 HARVEY, A. M., and JANEWAY, C. A. Development of acute hemolytic anemia, *Jr Am Med Assoc*, 1937, cix, 12.
- 2 WOOD, W. B., JR. Anemia during sulfanilamide therapy, *Jr Am Med Assoc*, 1938, cxi, 1916.
- 3 KOLETSKY, SIMON. Fatal hemolytic anemia following the administration of sulfanilamide, *Jr Am Med Assoc*, 1939, cxiii, 291.
- 4 WOOD, HAROLD. A fatality from acute hemolytic anemia which developed during the administration of sulfanilamide, *South Med Jr*, 1938, xxxi, 646.
- 5 RAVID, J. M., and CHESNER, H. Fatal case of hemolytic anemia and nephritic uremia following sulfapyridine administration, *Am Jr Med Sci*, 1940, cxcix, 380.
- 6 FOSBINDER, R. J., and WALTER, L. A. Sulfanilamide derivatives of heterocyclic amines, *Jr Am Chem Soc*, 1939, lxi, 2032.

- 7 LOTT, W A, and BERGEIM, F H 2-(-aminobenzenesulfonamide)-thiazole a new chemo-therapeutic agent, Jr Am Chem Soc, 1939, lxi, 3593
- 8 LONG, P H Sulfathiazole and sulfamethylthiazole, Jr Am Med Assoc, 1940, cxiv, 870
- 9 SPINK, WESLEY W, and HANSEN, ARILD E Sulfathiazole—clinical evaluation, Jr Am Med Assoc, 1940, cxv, 840
- 10 VAN DYKE, H B, GRECP, R O, RAKE, GEOFFREY, and MCKEE, CLARA M Observations on the toxicology of sulfathiazole and sulfapyridine, Proc. Soc Exper Biol and Med, 1939, xlii, 410
- 11 LONG, P H, HAVILAND, J W, and EDWARDS, LYDIA B Acute toxicity, absorption and excretion of sulfathiazole and certain of its derivatives, Proc Soc. Exper Biol and Med, 1940, xliii, 328
- 12 FLIPPIN, H F, SCHWARTZ, L, and ROSE, S B Comparative effectiveness and toxicity of sulfathiazole and sulfapyridine in pneumococcic pneumonia, ANN INT MED, 1940, xiii, 2038
- 13 OTTENBERG, R, and FOX, C L, JR Explanation for the cyanosis of sulfanilamide therapy, Proc Soc Exper Biol and Med, 1938, xxxviii, 479
- 14 FOX, C L, JR, HOGG, B, and OTTENBERG, R The occurrence of methemoglobinemia during therapy with sulfapyridine, sulfathiazole and sulfamethylthiazole, Jr Clin Invest, 1940, xix, 792
- 15 DE GOWIN, E L, WARNER, E D, and RANDALL, W L Renal insufficiency from blood transfusion, Arch Int Med, 1938, lxi, 609

AN INSTANCE OF CORONARY EMBOLISM IN SUBACUTE BACTERIAL ENDOCARDITIS *

By HARRY PARKS, M D, *Atlanta, Georgia*

IN recent literature on heart disease coronary thrombosis has occupied an increasingly important part of discussions on cardiac infarction. On the other hand, embolism of the coronary arteries with resultant cardiac infarction is infrequently mentioned. Up to 1933 Saphir¹ was able to find only 11 proved cases of this type, and to these he added three. During the last six years additional cases have been reported by Boger and Paradi,² Hoseason,³ and by Cobo, Quirno, and del Rio.⁴ The rare occurrence of coronary embolism is usually attributed to the anatomical situation of the coronary arteries. These vessels leave the aorta almost at right angles. Since the greatest velocity and bulk of the blood flow is in an upward direction, small particles leaving the left ventricle are likely to be swept far away from the mouth of the coronary arteries and do not often enter the coronary system. In the reported cases of coronary embolism, however, queer accidents have happened which have resulted in causing the lesion. In addition to coronary embolism caused by a vegetation set free from an active endocarditis or by a bit of clot breaking loose from an intramural thrombus, or by atheromatous material getting into the coronary vessels from the aorta, coronary embolism has been reported as due to fat, to air, to tumor cells or even to caseous tuberculous material.

* Received for publication December 9, 1939

From the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine, Boston

The following case is recorded to add one more case to the literature of subacute bacterial endocarditis in which death occurred as the result of coronary embolism

CASE REPORT

A 52 year old, white, Lithuanian housewife was admitted to the Robert Dawson Evans Memorial on September 20, 1938. She had been under the observation of various physicians for at least four years, consulting them because of progressive weakness, weight loss and pallor. Two years before entry she had weighed 91 kg (200 pounds), gradually losing until she weighed only 56 kg (123 pounds).

In 1935, three years before entry, Dr. Donato T. Scenna of Melrose, Mass., observed that she had an enlarged liver and spleen.

She entered the Robert Dawson Evans Memorial because of continued weakness. She admitted, too, that on exertion she now developed severe attacks of precordial pain or uncomfortable leg cramps.

She was poorly developed and nourished but she did not appear acutely ill. There was a peculiar reddish purple discoloration of the skin of the face, neck, and upper extremities, and marked pallor of the mucous membranes. No petechiae were observed. The pupils and pupillary reflexes were normal. The eye grounds had normal physiological cupping, and there were no hemorrhages or exudates. The heart on percussion appeared slightly enlarged. A soft precordial systolic murmur was noted, but no diastolic murmur was heard constantly. The blood pressure was 104 mm Hg systolic and 60 mm diastolic, and the pulse rate 80. The liver and spleen were greatly enlarged and firm in consistency. Several small axillary and inguinal lymph nodes were palpable. The remainder of the physical examination was not noteworthy.

Significant laboratory findings consisted of a well-marked hypochromic anemia, a normal white blood count and differential smear, a moderately low platelet count, a tendency to fixation of specific gravity of the urine, microscopic hematuria, a diminished phenolsulphonphthalein excretion, an elevated blood non-protein nitrogen level, hypoproteinemia with reversal of the albumin-globulin ratio, and achlorhydria to histamine stimulation. The blood Wassermann reaction was negative. Agglutination tests for typhoid, paratyphoid A and B and undulant fever were negative. A single blood culture showed no growth at the end of seven days. Urine specimens removed from each kidney were sterile on culture and microscopic examination. The venous pressure was 90 mm of water, and the circulation time by the Decholin taste method was 12 seconds. The basal metabolic rate was not elevated. An electrocardiogram made shortly after entry to the hospital showed regular sinus rhythm and normal P R intervals. Roentgen-ray and fluoroscopic examinations of the heart demonstrated calcification in the region of the aortic valve leaflets. Other roentgen-ray studies were not remarkable except for the incidental discovery of gall-stones.

The behavior of the patient's temperature was of interest. During the first three weeks of her stay in the hospital she was fever-free. During the following weeks of her illness she developed a low intermittent fever characterized by three or four days of normal temperature alternating with equal periods when the temperature rose to 99° or 100° F. During such febrile episodes there was no tachycardia, and electrocardiographic tracings remained normal.

No significant changes in symptoms or signs occurred until December 19, two and one half days before her death, and three months after her entry to the hospital. At about 10 o'clock in the evening, while lying in bed, she developed suddenly a violent nausea which was soon followed by sharp epigastric pain referred upward behind the sternum, but not radiating to the neck or arms. The pain was accompanied by vomiting. Approximately five hours after the onset of this attack, the temperature was 98° F, and the pulse rate was 90. There was a rise in blood pressure to 140 mm Hg systolic and 85 mm diastolic. Physical examination shortly after the

attack began revealed striking changes in the character of the heart sounds. There was now a loud blowing diastolic murmur audible over the base of the heart, loudest over the aortic area, and transmitted downwards toward the left sternal border where it was easily heard over the second and third intercostal spaces. The murmur in the apical region did not change. Marked epigastric tenderness was present which was thought to be due to enlargement of the liver. The lungs were clear. There was no edema. An electrocardiogram, made 12 hours after the attack began, showed changes in the precordial lead suggestive of myocardial infarction. This diagnosis was borne out subsequently by tracings taken at later intervals.

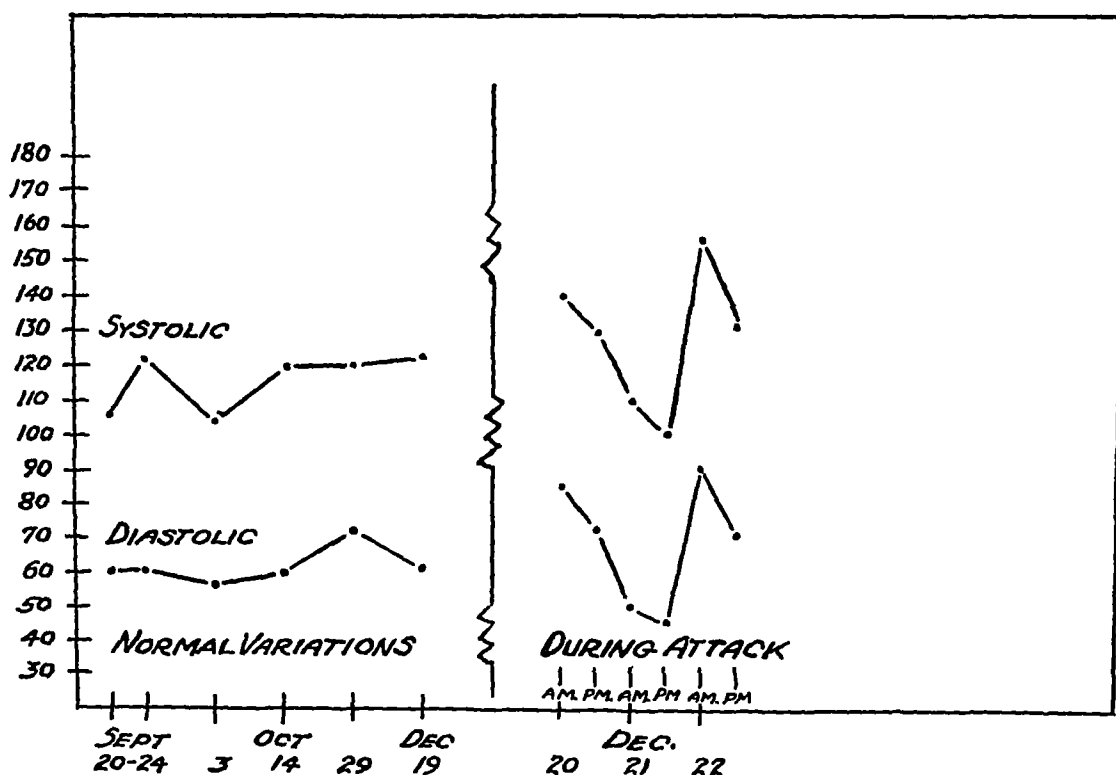


FIG 1 The blood pressure level in coronary thrombosis from embolism

During the first 48 hours after the onset of the cardiac infarction the temperature ranged from 99° to 100° F, and the pulse rate from 100 to 120. The respiratory rate rose to 28. The blood pressure soon fell to 100 mm Hg systolic and 45 mm diastolic. The patient grew worse rapidly. On the third day, 54 hours after the onset of pain, her temperature fell suddenly to 96° F, she developed diffuse cyanosis and marked air hunger. Curiously, the blood pressure now rose temporarily to 156 mm Hg systolic and 90 mm diastolic, although the heart sounds were distant and of very poor quality. The abdomen became distended. A little later the blood pressure again fell to 120 mm Hg systolic and 70 mm diastolic, and the heart began to fail rapidly, râles at the lung bases developed, and the neck veins became distended. A few hours before death the blood non-protein nitrogen concentration had risen to 100 mg per cent and the CO₂ combining power had fallen to 11 vol per cent.

At necropsy, the important findings concerned the heart, spleen and kidney. The pericardial sac contained about 15 c.c. of thick, flocculent, fibrino-purulent material. Culture of this fluid was negative. The visceral and parietal pericardial surfaces were smooth and glistening and showed only slight capillary engorgement. The heart

weighed 410 gm. The anterior descending branch of the left coronary artery in its terminal 4 cm stood out sharply as a dense, occluded, cord-like mass. The outer two-thirds of the left ventricular apex and the interventricular wall were soft and friable, and obviously infarcted. On the right posterior cusp of the aortic valve were soft, friable vegetations, longitudinally arranged, and measuring approximately 7 mm in length and 3 mm in width. Near the commissure of this leaflet was a small plaque of calcification 4 mm in diameter. The anterior surface of the left posterior valve was almost completely covered by soft, finger-like vegetations composed of fibrinous material. Extending outwards from the posterior surface of the cusp into this ma-

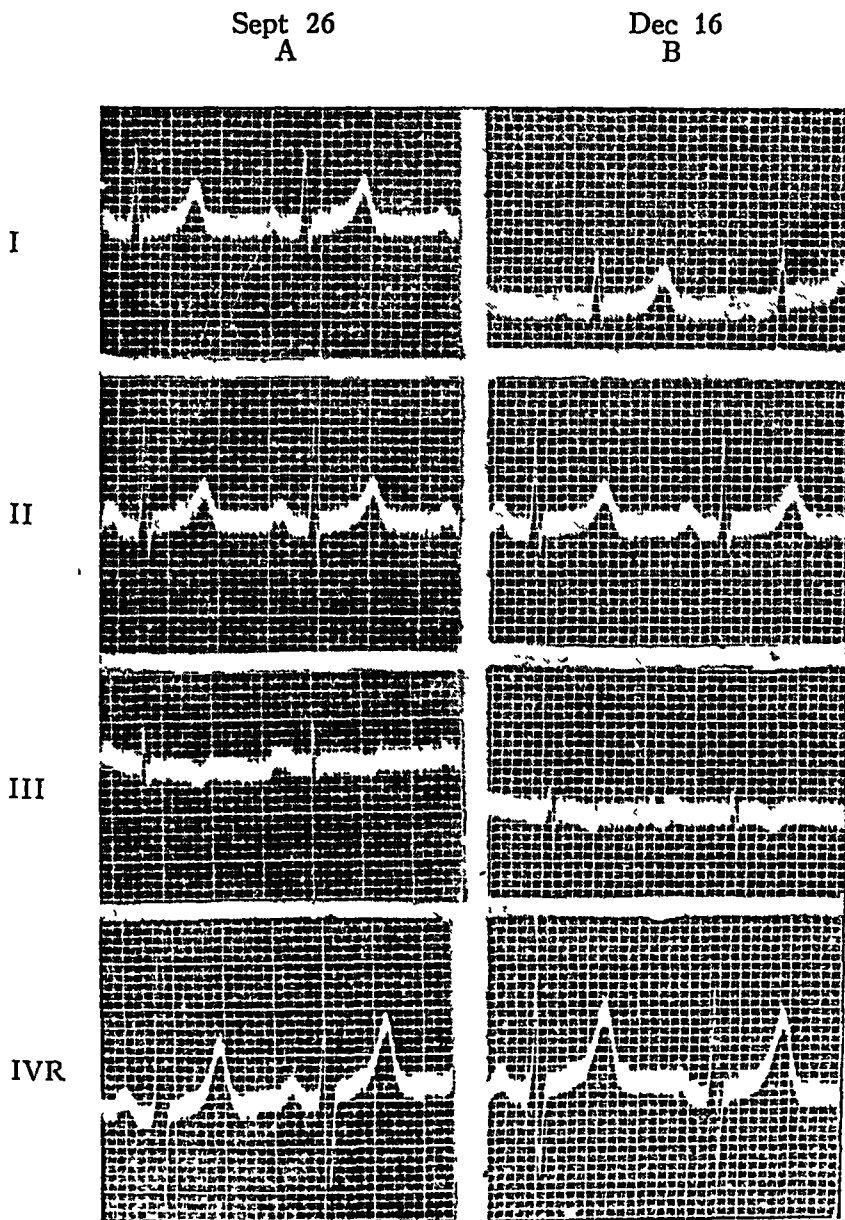


FIG 2 *A* and *B*, electrocardiograms made before the onset of coronary embolism show normal sinus rhythm and ventricular rate of 80. *C*, a tracing made 12 hours after the onset of coronary embolism shows decrease in voltage of QRS complexes in all the leads, nearly complete disappearance of R_1 , flattening of T_1 , changes in direction of T_2 from negative to positive, high take-off of ST_1 , and sinus tachycardia with ventricular rate of 120. *D*, a tracing made four hours later shows little change except decrease in depth of S_1 . The ventricular rate is 140. *E*, a tracing made 38 hours after the onset of coronary embolism shows a slurred S_1 and Q_2 , flattening of T_1 , isoelectric T_2 , inversion of T_3 , decrease in take-off of ST_1 , with inversion of T_4 , upward convexity of ST_4 , and sinus tachycardia with ventricular rate of 120.

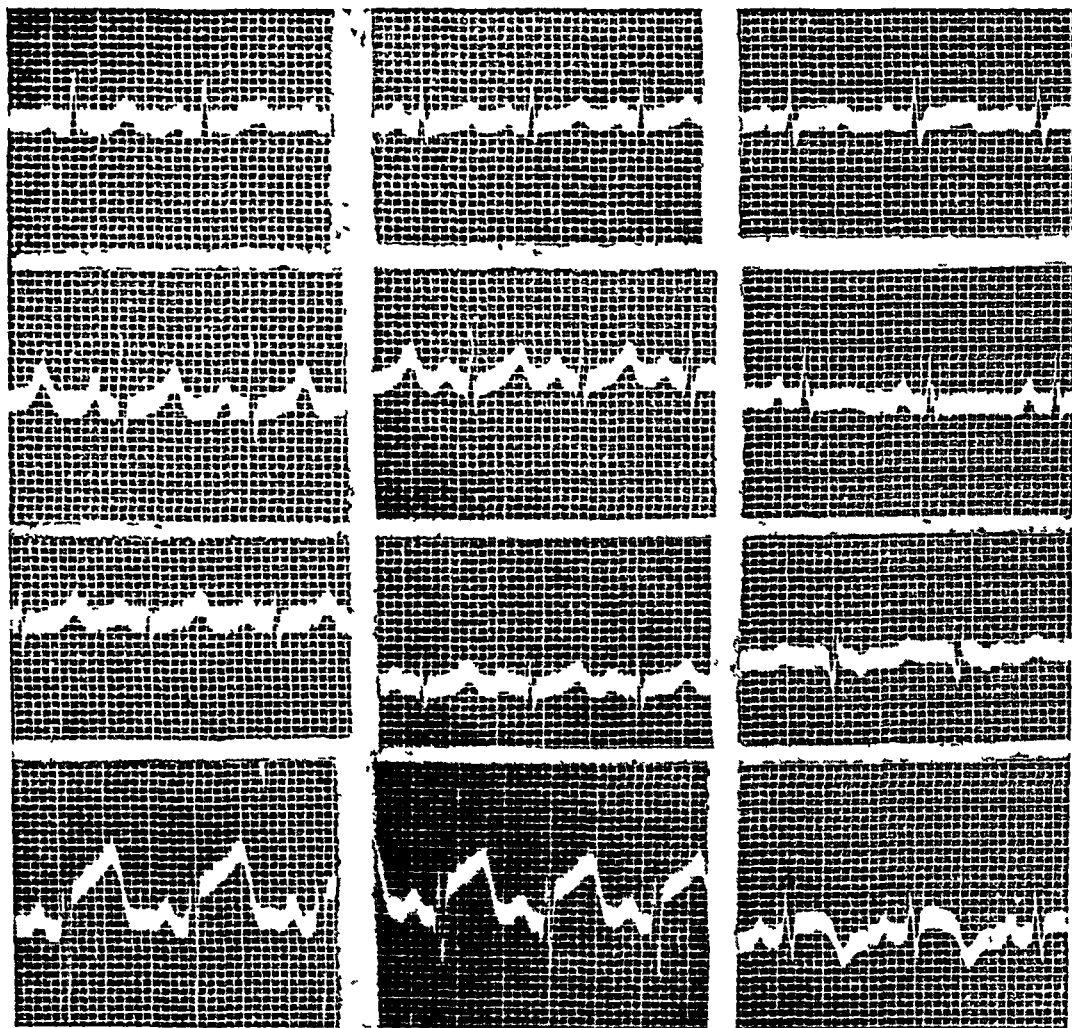
Dec 20
12 Hrs
CDec 20
16 Hrs
DDec 21
38 Hrs
E

FIG 2 (continued)

terial and forming a cup-like entity 4 mm in diameter was a mycotic aneurysm of the valve leaflet. The anterior valve leaflet presented a similar excavation measuring 5 mm in diameter, its outer anterior surface also was covered with necrotic fibrinous material. The pulmonary and tricuspid valves were entirely normal. At the base of the mitral valve there were atheromatous deposits and beginning calcification of the mitral ring.

The orifices of the coronary arteries were normally placed and widely patent. The immediately adjacent intima showed well-defined early vegetative lesions which were so minute that they were discernible only with the aid of a hand lens. These were in no way occlusive in nature. The coronary arteries on gross examination were remarkably free from any atheromatous lesions or evidence of fibrosis. The anterior descending branch of the left coronary artery at a point approximately 4 cm from the apex was occluded by a firm, dry, somewhat friable embolus measuring approximately 1 cm in length. This was partially adherent to the vessel wall. On either

side of the embolus the vessel was free of any obstruction, and the vessel wall appeared normal

Microscopic examination of a section through the aortic valve cusp at one of the pouch-like areas showed a well-defined mycotic aneurysm within which was a large amount of partially organized blood-clot. In and about this were many colonies of

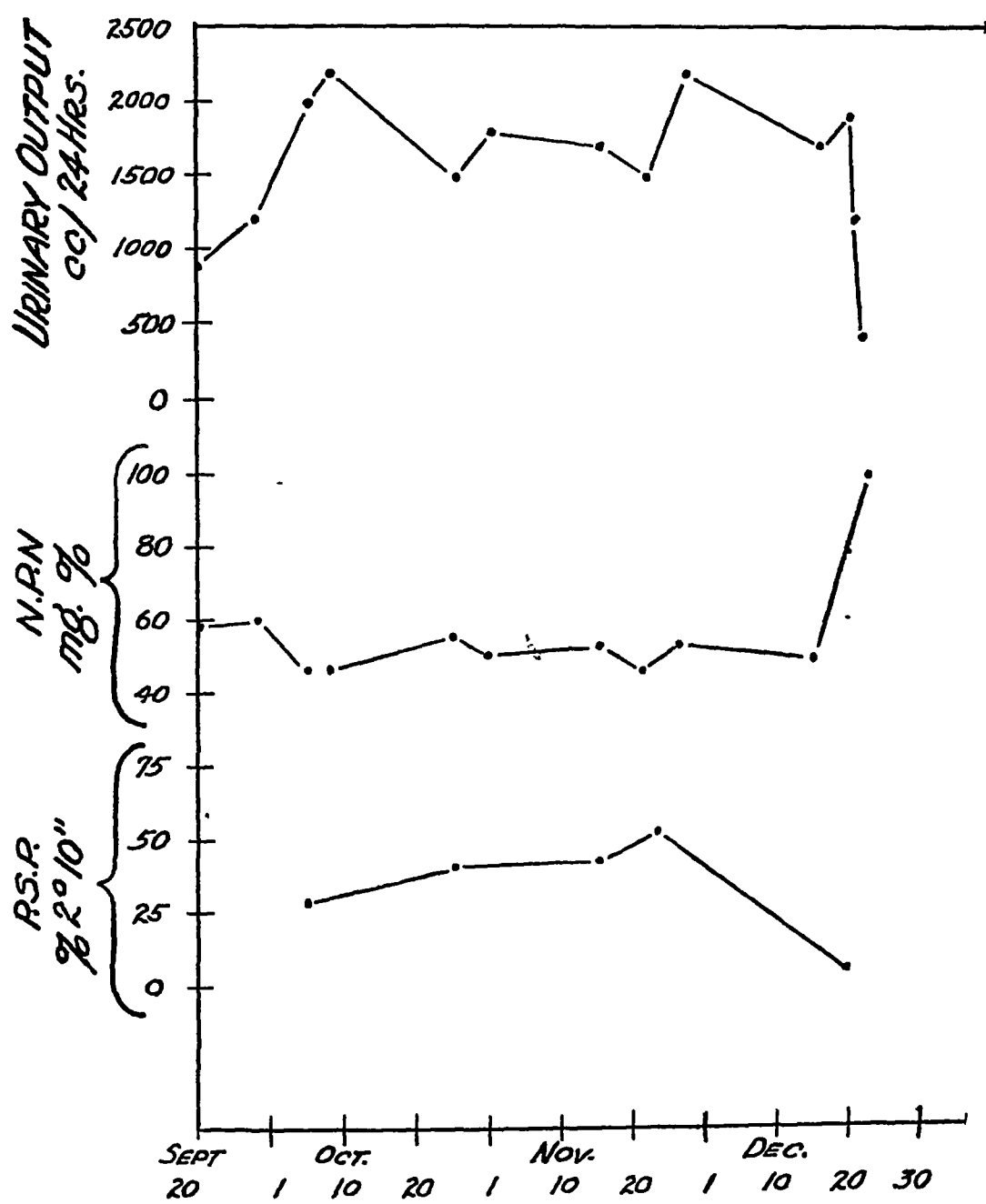


FIG 3 The blood non-protein nitrogen, the urinary output, and phenolsulphonphthalein output in coronary embolism

streptococci. The larger coronaries showed only moderate fibrous and hyaline thickening of the intima. In the occluded area there was a thrombus which appeared to have developed from an embolus set free from one of the vegetations on the aortic valve leaflets.

The aorta showed rare small atheromatous plaques throughout its entire course.

with one area of calcification just above its bifurcation. There was no evidence of thromboses or emboli in any of the larger vessels.

The spleen weighed 780 gm and was dark reddish to purplish-gray in color. In the upper pole was an old infarct which was roughly 4 cm in diameter.

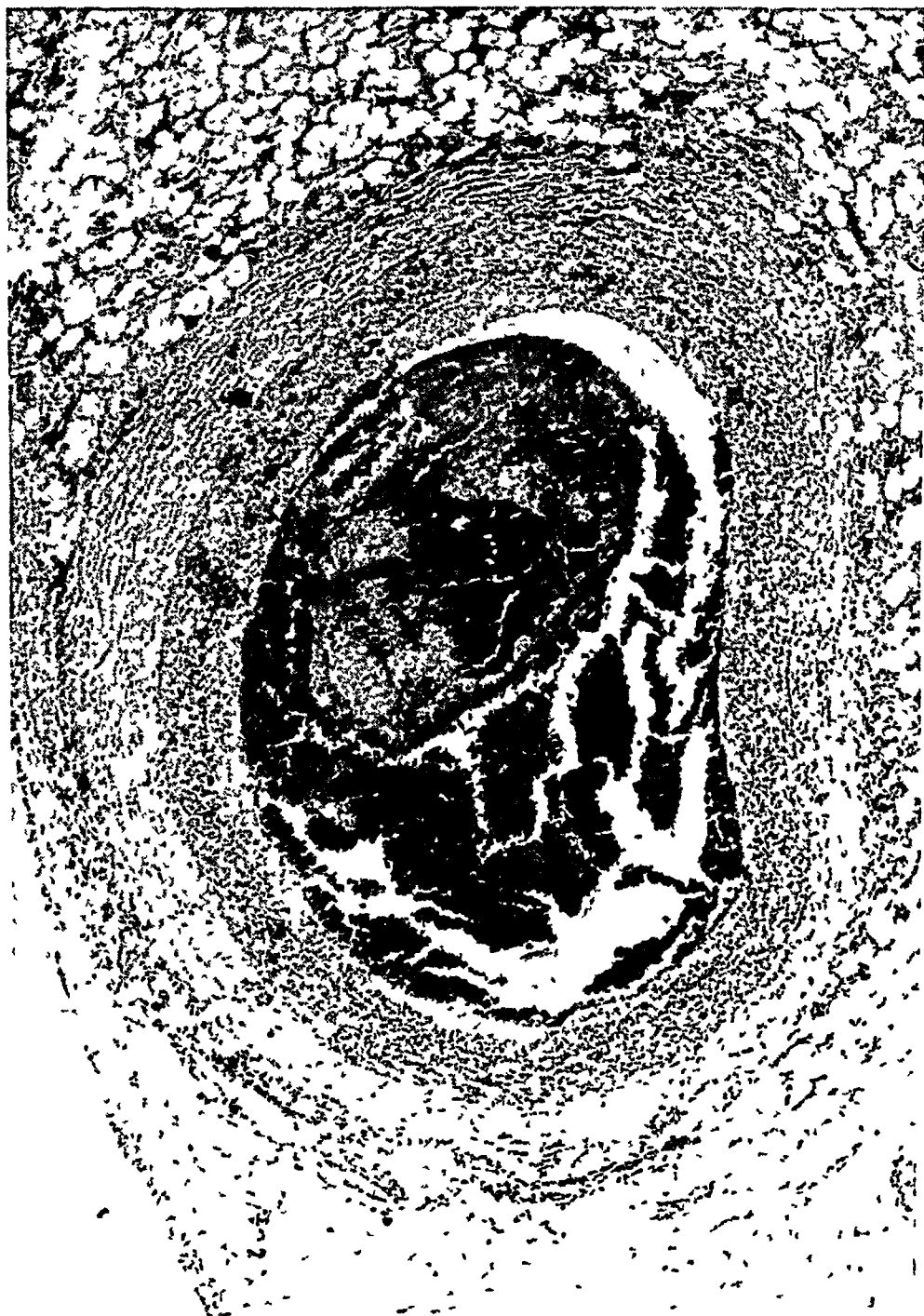


FIG 4 Photograph of the heart showing the cusps of the aortic valve with vegetations. The retracted cusp on the right shows vegetations on the upper surface of the leaflet and a mycotic aneurysm.

The kidneys together weighed 290 gm. The renal cortex was stippled with many minute, punctate, bright red dots. On histological study many of the glomeruli showed embolic glomerular lesions, the tubules contained a large number of blood casts, hyaline and granular debris.

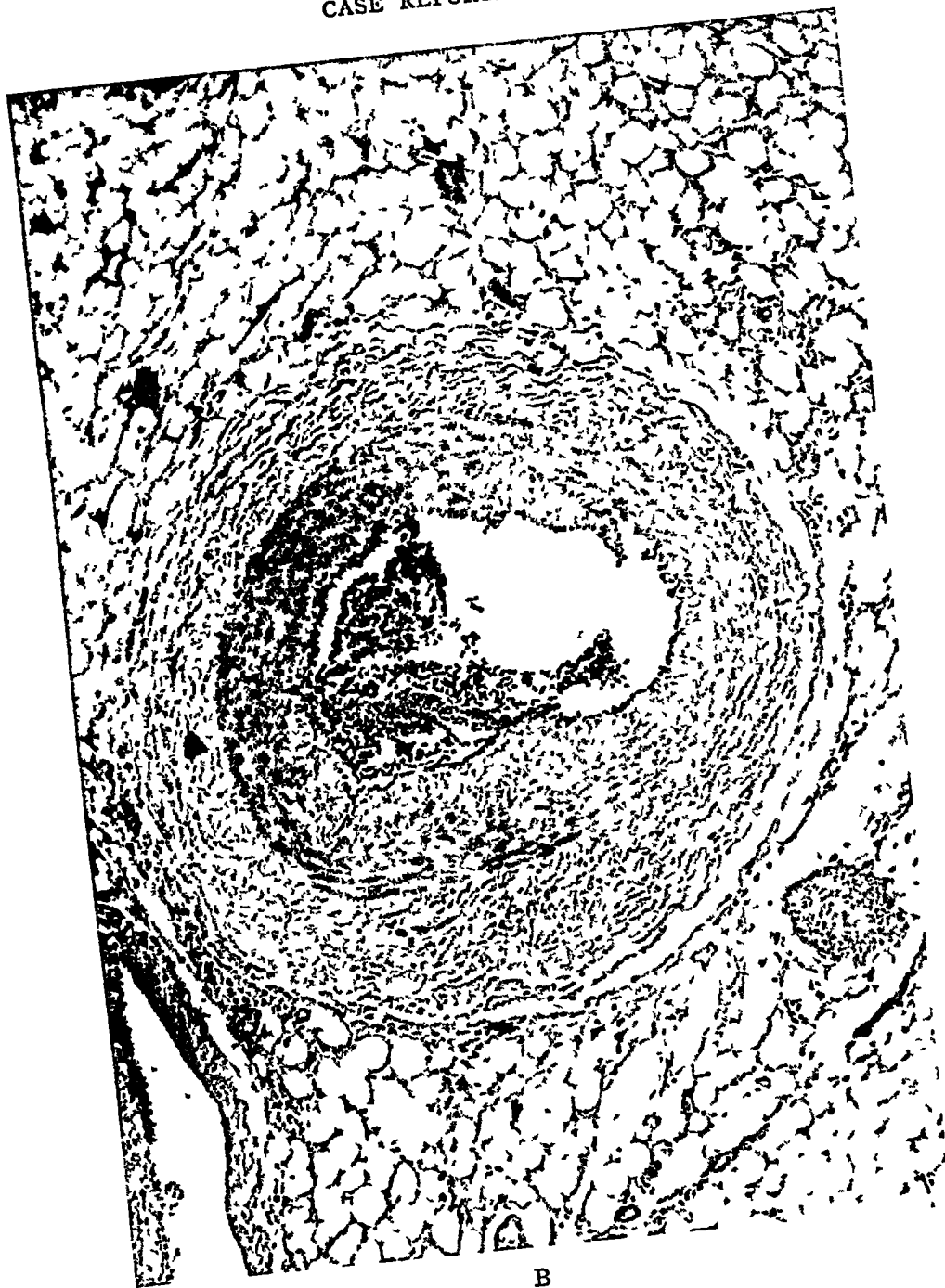
Virchow⁶ is given credit for having first described coronary embolism. In 1856 he reported the case of a 27 year old girl who had endocarditis of the mitral valve with emboli to the coronary arteries. Saphir, as has been already

mentioned, in 1933 reviewed the literature of coronary embolism up to that time and found only 11 acceptable cases. In these, embolism was found to occur most frequently in the left coronary artery or its branches, and sudden death practically always resulted. The youngest patient noted by him was a case of Rolleston's, a 17 year old boy who died suddenly from an embolus in the de-



A

FIG 5 The coronary artery. A Photomicrograph of the artery approximately 4 cm. from the apex. The embolus shows no organization. There is early neutrophilic infiltration of the vessel wall. $\times 50$. B The same vessel 1 cm. lower. $\times 50$. The vessel wall appears normal.



B

FIG 5 (continued)

scending branch of the left coronary artery which originated from a thrombus in the left ventricle

Since Saphir's review additional reports of coronary embolism have appeared occasionally. Hoseason reported a 36 year old patient who collapsed in the street while walking to work. At necropsy, he was found to have left ventricular hypertrophy. The aortic valves were calcified. On the right posterior aortic cusp a thrombus was loosely attached to an ulcerated area over a calcified nodule

One-half inch along the right coronary artery was a small particle of vegetation which was thought to have originated from the ulcerated valve cusp. Boger and Paradi reported the case of an 18 year old woman with subacute bacterial endocarditis. She suddenly developed intensive oppression and chest pain, tachycardia, weak pulse, poor heart sounds, labored respiration and cyanosis, and died in a few minutes. Necropsy demonstrated an endocarditis of the mitral valve with a fresh embolus in the left coronary artery. The ventricle did not show infarction, apparently because of the suddenness of death.

Cobo, Quirno and del Rio described the case of a woman 36 years old who developed gripping precordial pain after getting up quickly from the table. The pain increased in intensity, and soon she complained of palpitation and a sense of impending death. Physical examination showed a soft presystolic murmur in the mitral area. There were no thrills. Electrocardiographic tracings gave findings characteristic of coronary occlusion. On the second day of the patient's illness, she developed signs of frank cardiac insufficiency and died on the third day after the onset of the attack. Necropsy revealed several small yellowish-white vegetations on the mitral valve. These were friable and varied in size. The left coronary artery and its branches were normal. In the right coronary artery was a small embolus firmly adherent to the wall of the vessel. This was thought to resemble in character the vegetations on the mitral valve.

Our case appears unusual in several ways. In the first place the latency of the endocarditis was striking. The patient had been seen in various clinics during her prolonged illness and always her marked anemia and huge spleen attracted attention. No one paid any particular attention to the cardiac and renal findings.

In the second place the behavior of the blood pressure at the time of the coronary embolism is worth emphasizing. It has already been pointed out by Fitz,⁶ Wood and Wolferth,⁷ and others that an initial rise followed by a fall in blood pressure may take place in acute occlusive coronary lesions. In our case an initial rise, then a fall, and finally a second rise and fall in blood pressure occurred, the highest reading being obtained shortly before death.

The marked terminal rise in the blood non-protein nitrogen level which was observed in our case has been noted in other cases by Steinberg,⁸ and by Jeghers and Bakst.⁹ Presumably the rise was due to dehydration, oliguria, and other extrarenal factors superimposed on an already existing nephritis. As in other cases the rapid accumulation of non-protein nitrogen in the blood was an ominous sign.

On the whole the case is reported as representing an example of a chronic form of subacute bacterial endocarditis with a notable splenomegaly, anemia, and characteristic pathologic findings in heart and kidney. Death resulted from cardiac infarction due, we believe, to coronary embolism. Coronary embolism as a complication of subacute bacterial endocarditis occurs infrequently, but when it does occur it may induce a striking sequence of clinical events.

REFERENCES

- 1 SAPHIR, O. Coronary embolism, *Am Heart Jr*, 1933, viii, 312-322
- 2 BOGER, A., and PARADI, G. W. Coronarembolie, *Klin Wchnschr*, 1934, xiii, 724-726
- 3 HOSFASON, A. S. Coronary embolism, *Lancet*, 1935, i, 928-930

- 4 COBO, J L, JR, QUIRNO, N, and DEL RIO, J G Case of occlusion of right coronary artery due to embolism, importance of breast-shoulder lead (Lead IV) for exact diagnosis of occlusion, *Rev argent de cardiol*, 1935, II, 248-263
- 5 VIRCHOW, R Ueber capillare Embolie, *Virchow's Arch f path Anat*, 1856, IX, 307
- 6 FITZ, R A case of angina pectoris with cardiac infarct induced by the intravenous injection of sodium tetraiodophenolphthalein, and followed by relief of anginal symptoms, *Trans Assoc Am Phys*, 1928, XLIII, 292
- 7 WOOD, F C, and WOLFERTH, C C Angina pectoris The clinical and electrocardiographic phenomena of the attack and their comparison with effects of experimental coronary occlusion, *Arch Int Med*, 1931, XLVII, 339
- 8 STEINBERG, C L The prognosis of coronary thrombosis based on the non-protein nitrogen in the blood, *Jr Lab and Clin Med*, 1934, XX, 279-287
- 9 JEGHERS, H, and BAKST, H J The syndrome of extrarenal azotemia, *ANN INT MED*, 1938, XI, 1861-1899

SPONTANEOUS HEMOPNEUMOTHORAX, REPORT OF A CASE*

By DANIEL SNIVELY, M D, HARRY SHUMAN, M D, F A C P, and WILLIAM D SNIVELY, M D, *Rock Island, Illinois*

SPONTANEOUS hemopneumothorax, judging by the number of case reports, is a rare condition Hopkins,¹ reviewing the literature in 1937, found 46 cases reported since 1900 This entity apparently represents a spontaneous pneumothorax in which some unusual condition is present to give rise to bleeding into the pleural cavity It must be distinguished from traumatic hemopneumothorax and from the effusion of bloodstained serum occasionally seen in malignant growths of the lung and pleura

Our patient presented a classical example of spontaneous hemopneumothorax Although a total of over 1400 cubic centimeters of blood was removed from his pleural cavity, he made a reasonably uneventful recovery Because of the known value of sulfanilamide in keeping stored blood sterile, this drug was given the patient by mouth and may have assisted in preventing infection of the blood present in the pleural cavity We were interested to observe the correlation between the sedimentation rate and the amount of blood remaining in the pleural cavity, shown by serial sedimentation rate determinations and chest roentgenograms taken concomitantly

CASE REPORT

The patient, E C, was first seen on March 20, 1940 with the history that eight days previously he had experienced the sudden onset of an excruciating pain in the right side of the chest while at school He felt quite weak and was taken home Upon reaching home he fainted He revived quickly but was dyspneic, orthopneic, and developed a dry hacking cough He remained in bed His mother stated that when moving him she could hear a splashing sound He complained of a frontal headache which was constant Epistaxis occurred twice during the eight day period Fever ranging between 100° and 102° F was present

The patient's previous health had been good He had been wrestling about

* Received for publication October 8, 1940

two months previous to the above event and had experienced a pain low in the right chest. This pain was not severe and had disappeared after several weeks. A careful physical examination about a week before the onset of the illness was negative. The family history revealed that the patient's aunt had had tuberculosis.

Physical examination revealed a pale asthenic youth who appeared quite ill. Dyspnea was marked and the patient was unable to stand for any time without sup-



FIG 1 Anteroposterior roentgenographic view of the chest taken in the recumbent position with the use of a Potter-Bucky diaphragm on April 15. Shows a marked effusion in the right pleural cavity extending upward to the level of the third interspace. The sedimentation rate at this time was 45 millimeters in 1 hour.

port. The temperature was 100.5° F. The area representing the base of the right lung was flat to percussion and the interspaces on the right side of the chest were full. The apex beat was 4.5 centimeters to the left of the nipple line. No breath sounds were audible over the lower two-thirds of the right lung. Fluoroscopic examination revealed complete density of the lower three-fourths of the right chest cavity with a horizontal fluid level indicating pneumothorax. The red blood count was 4,460,000,

CASE REPORTS

the white count 25,600, and the hemoglobin 65 per cent Wasseimann and Kahn tests were negative

Under local anesthesia thoracentesis was performed in the seventh interspace posteriorly on the right side Pure blood was obtained The needle was withdrawn and reinserted in a different location to rule out the possibility of venepuncture Blood was obtained in this area also About 450 c c of non-clotting blood were then

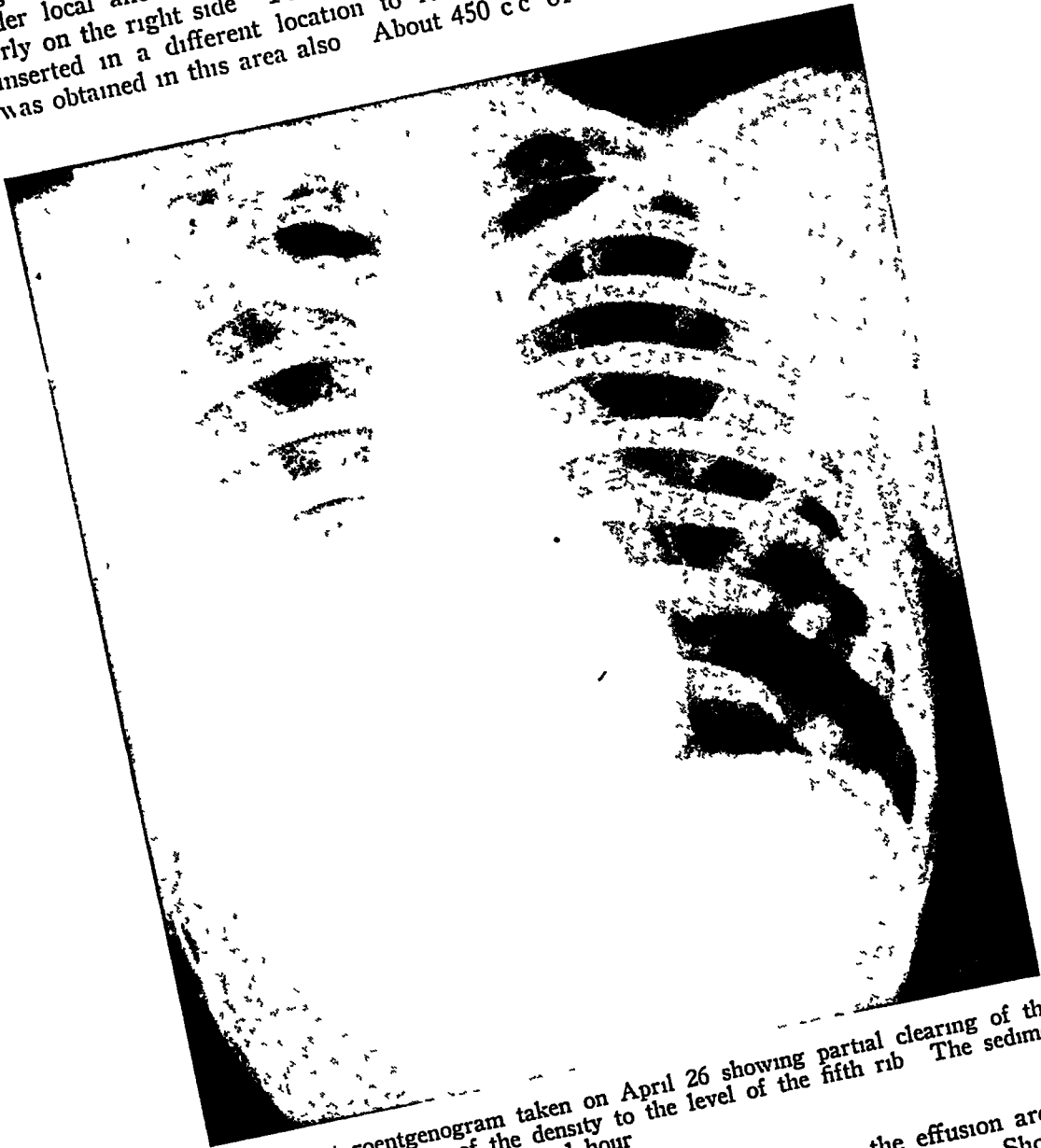


FIG 2 Chest roentgenogram taken on April 26 showing partial clearing of the right pleural cavity and reduction of the density to the level of the fifth rib The sedimentation rate at this time was 23 millimeters in 1 hour

removed by aspiration Air was found to be present above the effusion area The patient experienced some relief from dyspnea but was extremely weak Shock treatment was given The fluid removed from the pleural cavity appeared like normal blood except that it did not clot The hemoglobin content was 65 per cent, exactly that of the blood specimen obtained from the patient's finger

During the following three weeks the patient made excellent progress Dyspnea and orthopnea were markedly relieved following the tap Sulfanilamide was admin-

present
effusion on
The sedi

of the right
chest were full
of breath sound
examination
with a

istered in an effort to prevent infection of the blood remaining in the pleural cavity. However, the patient continued to run a low grade fever for two weeks. Hematinics were administered and the red cell count rose. The white count decreased.

On April 1 fluoroscopy revealed a basal shadow on the right but no fluid level. The temperature was 98.6°F , and the hemoglobin 80 per cent. Thoracentesis was performed, and 1050 cc of non-clotting blood were withdrawn. The patient stood the

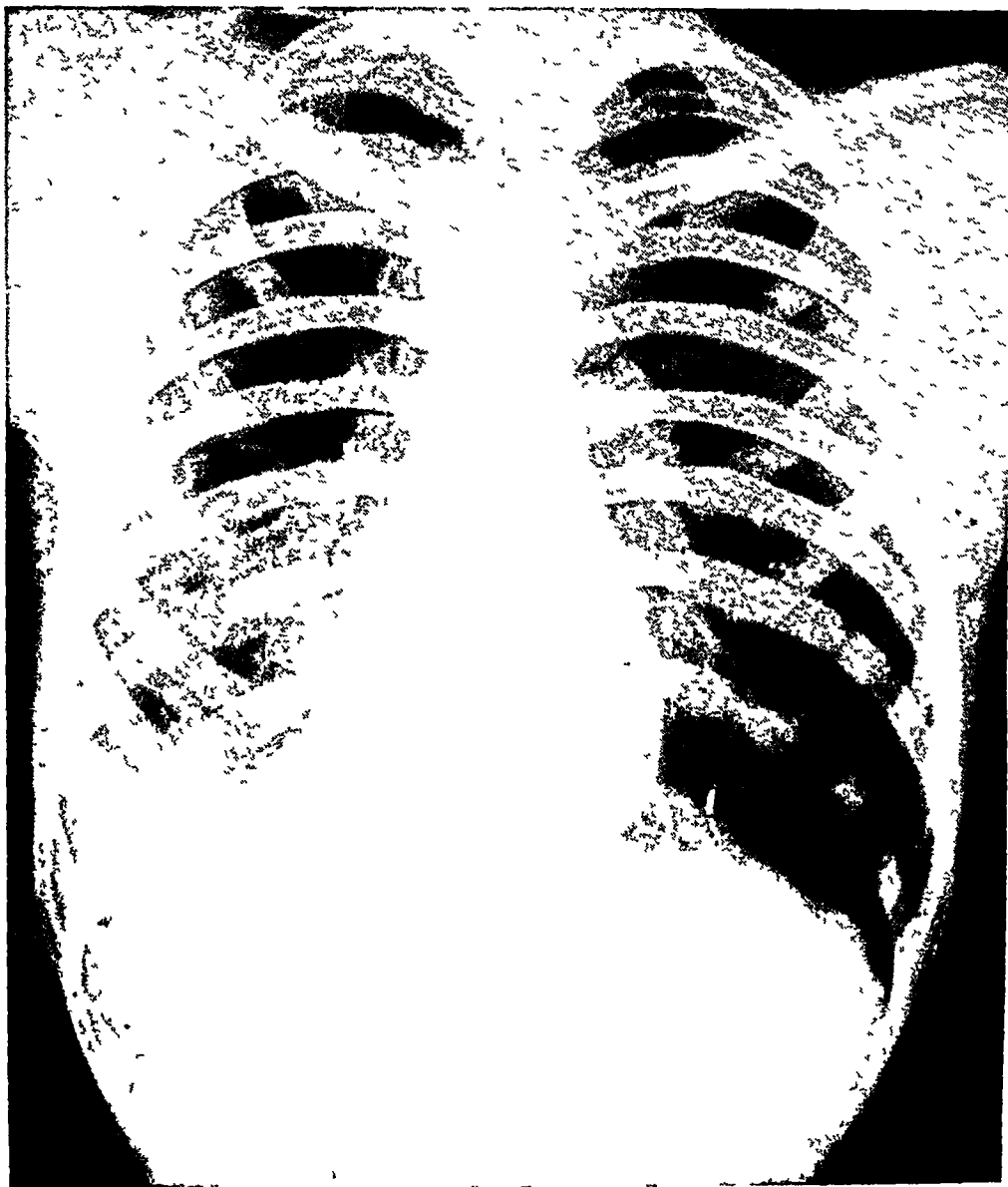


FIG 3 Chest roentgenogram taken on May 20 revealing practically complete evacuation of the effusion. Both lung fields appear normal but there is fixation of the right leaf of the diaphragm. The sedimentation rate was 5 millimeters in 1 hour (normal).

procedure well. Fluoroscopy following the tap revealed persistence of the shadow over the right lung base but lessening of its density. Continued improvement followed the procedure.

On April 15 a chest roentgenogram, taken in the recumbent position with the use of a Potter-Bucky diaphragm, revealed marked effusion in the right pleural cavity to the level of the third interspace (figure 1). The sedimentation rate was 45 millimeters in one hour. The urine at this time was found to contain albumin.

Bence-Jones protein was absent and the glucose test and microscopic examination were negative

A chest roentgenogram on April 29 revealed clearing of the right pleural cavity and reduction of the density to the level of the fifth rib. The left thoracic cavity was normal in appearance (figure 2). The sedimentation rate was 23 millimeters in one hour. The hemoglobin at this time was 80 per cent.

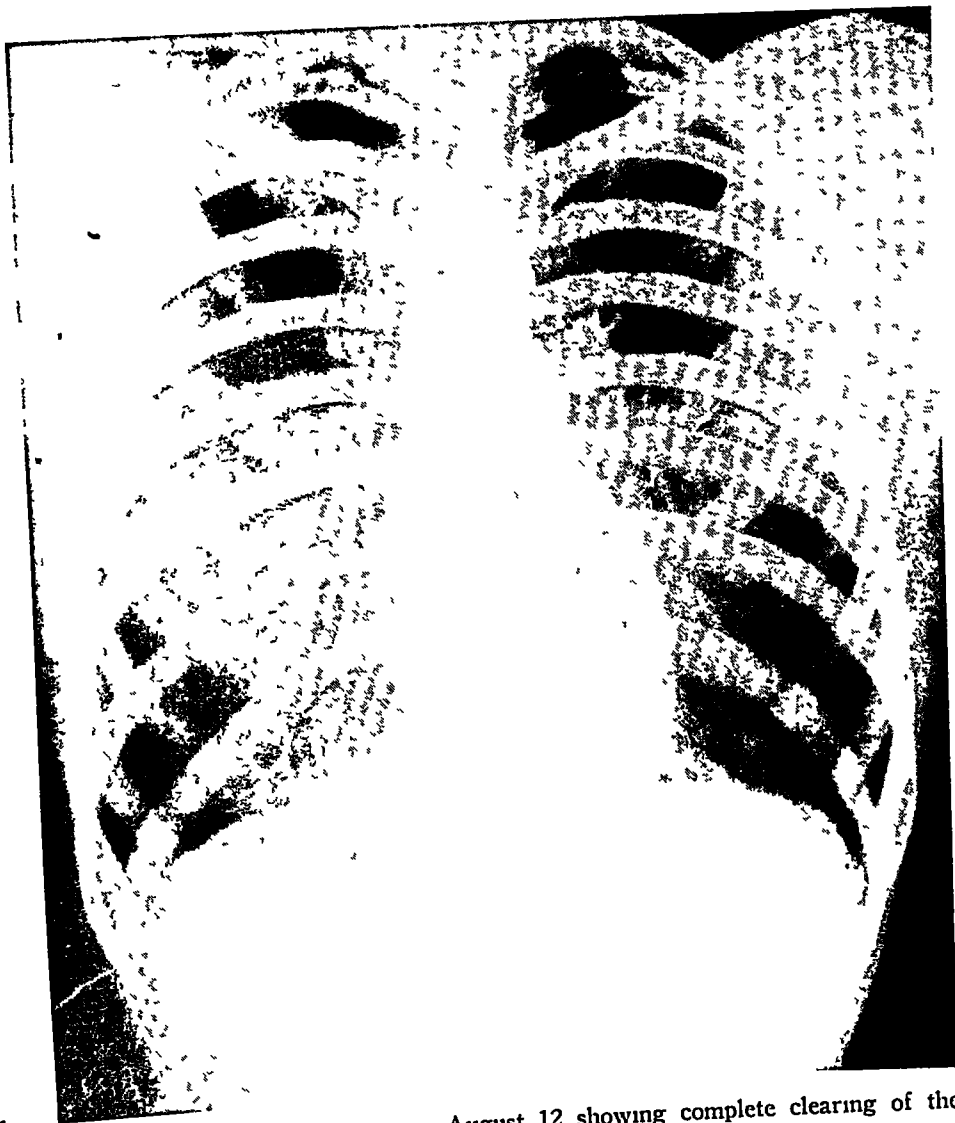


FIG 4 Chest roentgenogram taken on August 12 showing complete clearing of the right costo-phrenic angle and normal lung fields

On May 20 a chest roentgenogram revealed practically complete evacuation of the fluid. Both lung fields appeared normal, but there was fixation of the right leaf of the diaphragm (figure 3). The sedimentation rate was 5 millimeters in one hour.

Repeated fluoroscopic examinations in the succeeding weeks revealed gradual clearing of the right costo-phrenic angle. On August 12 the right leaf of the diaphragm showed normal excursion, complete clearing of the right costo-phrenic angle, and normal lung fields (figure 4). At this time the patient stated that he was feeling very well and had no complaints.

COMMENT

Hemopneumothorax may occur as a result of trauma or it may occur as a complication during artificial pneumothorax, as reported by Hurst and Epstein² These types of hemopneumothorax are not to be classed as spontaneous Frey³ classified as spontaneous those cases in which there was a lack of a definite cause, such as demonstrable disease or trauma

The majority of cases of spontaneous hemopneumothorax occur in individuals previously in good health In an analysis of 17 cases Jones and Gilbert⁴ found the age limits to be 17 and 44 years In over half of the cases the condition had occurred in the third decade All of these patients were males As Hopkins¹ points out, the disproportionate incidence in males is difficult to explain If the condition is due to developmental defects, he reasons, these should occur in females as frequently as in males If latent tuberculosis were a factor the incidence should be higher in women If physical activity were important the increasing participation of women in strenuous sports and occupations should cause an increasing incidence in females This, apparently, has not occurred

As regards the mechanism of production of spontaneous hemopneumothorax, the consensus is that it probably consists of the rupture of an emphysematous air vesicle lying beneath the pleura, followed by the tearing of pleural adhesions containing blood vessels

Birch⁵ reported the findings at postmortem examination in a fatal case of spontaneous hemopneumothorax as follows "The right pleural cavity contained several pints of fluid blood and some air There was a minute tuberculous cavity at the apex of the right lung, but it had not ruptured There were no emphysematous blebs On the anterior surface of the right upper lobe there was a roughened area of pleura and bleeding and escape of air had apparently originated here, but there was no gross macroscopic change Apart from the minute cavity there was no other evidence of tuberculosis in the right lung The other lung and the rest of the body were quite normal" Birch⁵ mentions the findings in five previously autopsied cases In the first a torn adhesion to an emphysematous bulla was found There was no evidence of tuberculosis In the second the cause of bleeding was not ascertained In the third, torn adhesions to subpleural blebs were found, associated with a puckered tuberculosis scar In the fourth case a torn emphysematous bleb was present at the apex, the edges of the tear being covered with coagulated blood There was no evidence elsewhere in the lungs of tuberculosis or emphysema In the fifth case a ruptured bulla was found, but there was no evidence of tuberculosis

In a case described by Housden and Piggot⁶ "necropsy revealed the presence of a firm pleural adhesion attached to an emphysematous cavity at the apex of the left lung The adhesion appeared to have been torn away from the chest wall during life, and it seems quite possible that it was from the torn adhesion that bleeding took place"

The symptomatology of spontaneous hemopneumothorax is that of spontaneous pneumothorax combined with the symptoms of hemorrhage and of pleural effusion The clinical picture in a given case will depend upon the relative parts which these factors play As Head⁷ states, the loss of blood is both complicated and aggravated by the collapse of the lung and by the resultant

pressure on the heart and great veins. The initial pain may occur while the patient is at rest or it may follow slight exertion. It is usually localized at first but later may involve the entire side of the chest or even the abdomen. Thus Milhorat⁸ reported a case of spontaneous hemopneumothorax in which the abdominal signs simulated those of an acute surgical abdomen. In reviewing the literature Hopkins¹ found that in many cases there has been noted a second sharp attack of pain occurring from a few hours to several days after the original onset of pain. This has been followed by signs of effusion. If the bleeding is slow, signs of hemorrhage may be mild or may never appear. In several cases blood has been discovered as an incidental finding.

Treatment will vary considerably with the individual case. If the amount of blood in the pleural cavity is slight, thoracentesis may be delayed. If fluid is present in such large amounts as to cause pressure symptoms, however, it should be withdrawn. In view of the possibility that calcification of the pleura or other complications may result, should a considerable quantity of blood be allowed to remain in the pleural cavity, it would seem wise to prevent such an occurrence by thoracentesis as indicated. However, as Louria⁹ aptly states, complete drainage of the pleural cavity or the reduction of the intrapleural pressure to a distinctly negative level may result in further bleeding or in the opening up of a partly closed bronchopleural fistulous tract.

It is of obvious importance in the management of a case of hemopneumothorax to determine whether or not the hemorrhage is progressing. Korol¹⁰ suggests that if the aspirating needle is blocked by clots, or if the aspirated blood clots in the basin, one may infer that hemorrhage continues. As the cell count of the fluid varies with the site of puncture and the position of the patient, serial blood counts on aspirated fluid may be of no help in determining the persistence of hemorrhage. Of obvious importance are frequent blood counts on capillary blood, blood pressure examinations, and serial chest roentgenograms or fluoroscopic examinations. We found a definite correlation between the amount of blood present in the pleural cavity as revealed by chest roentgenograms and the sedimentation rate (figures 1 to 4).

Korol¹⁰ suggests that in cases in which bleeding continues and there is danger of exsanguination, a thoracoscope should be introduced into the pleural cavity and the bleeding vessel cauterized, after aspiration of the pleural contents.

Although recurrence of spontaneous pneumothorax is well known, there are no recorded cases of recurrent spontaneous hemopneumothorax. It seems likely that pleural adhesions following the presence of blood in the cavity make further collapse and bleeding impossible.

REFERENCES

- 1 HOPKINS, HENRY U. Spontaneous hemopneumothorax, *Am Jr Med Sci*, 1937, cxciii, 763.
- 2 HURST, ALIEN, and EPSTEIN, HARRY H. Massive intrapleural hemorrhage as a complication of artificial pneumothorax, *Quart Bull Sea View Hospital*, 1937, ii, 155.
- 3 FREY, JOSEPH L. A case of spontaneous hemopneumothorax, *Jr Am Med Assoc*, 1935, civ, 1305.
- 4 JONES, OSWALD R., and GILBERT, CHARLES LOUIS. Spontaneous haemopneumothorax, *Am Rev Tuberc*, 1936, xxxiii, 165.
- 5 BIRCH, C. ALAN. A fatal case of spontaneous haemopneumothorax, *Brit Jr Tuberc*, 1936, xxx, 99.

- 6 HOUSDEN, E GERARD, and PIGGOT, ALLEN Spontaneous hemopneumothorax with unusual post-mortem findings, Brit Med Jr, 1931, ii, 941
- 7 HEAD, JEROME R Hemorrhage into the pleural cavity, Surg, Gynec and Obst, 1937, lxxv, 485
- 8 MILHORAT, A T A case of spontaneous hemopneumothorax (with some simulation of an acute surgical abdominal condition), Am Jr Surg, 1931, xiii, 315
- 9 LOURIA, MILTON R Spontaneous hemopneumothorax with report of five cases and one autopsy, Quart Bull Sea View Hosp, 1938, iv, 44
- 10 KOROL, EPHRAIM Haemorrhagic pleurisy of tuberculous origin and haemopneumothorax, Am Rev Tuberc, 1936, xxxiii, 185

SULFONAMIDES AND HEPARIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS *

By LEO WAITZKIN, RICHARD H SMITH, and WALTER B MARTIN, F A C P,
Norfolk, Virginia

THE sulfonamides and heparin have been among the most recent forms of therapy in subacute bacterial endocarditis. Concerning the value of the sulfonamides there are widely divergent opinions. Some are to the effect that they are of doubtful or no value, others that recoveries may be definitely ascribed to their usage^{1, 2, 3, 4, 5, 6, 10}. Concerning heparin in conjunction with sulfapyridine, no optimistic conclusions have been expressed since the sanguine preliminary report by Kelson and White⁷.

A consideration of factors involved in subacute bacterial endocarditis clarifies the reasons advanced for the employment of heparin and sulfonamide compounds, and also suggests explanations for the results.

Streptococcus viridans appears to be not a species but a heterogeneous group of cocci widely dissimilar in many ways. Some strains are resistant and others susceptible to the sulfonamides⁸. It has been suggested⁸ that it might be worth while, before embarking on a course of treatment, to determine by cultural methods the degree of susceptibility of the patient's streptococcus to the action of sulfonamides.

The bacteria accumulate within the valve cusp's margin where no blood vessels penetrate, and so are safe from attack by leukocytes from within (leukocytes being the chief agents of destruction of the *Streptococcus viridans*) and secure from antibodies and chemotherapeutic substances in the blood bathing the valve from without. Should the bacteria migrate toward the valve base where blood vessels penetrate, they face destruction by leukocytes. Should they erupt through the valve edge, they are exposed to the blood stream or swept into it, and may be destroyed. Fibrin and platelets are deposited at the damaged site, providing for the remaining bacteria an ideal culture medium and a barrier against the blood stream that is absolutely impenetrable⁹. Spreading outward, at the vegetation's base, there is almost always a reparative fibrosis. Should these processes of defense and healing outstrip the processes of bacterial multiplication and thrombotic formation, healing would ensue.

* Received for publication September 29, 1941

To aid these natural processes, the sulfonamides have been employed for their bacteriostatic and possible bactericidal action. The theory has been advanced that, during sulfonamide administration, "all of the preexisting thrombi should become organized into fibrous scar tissue, while all newly formed thrombi in a patient under active treatment will be impregnated with the drug. Thus conditions will tend to become less and less favorable for growth of the organism if an effectual drug is taken continuously over a long period of time"⁹ It is not yet clear which of the sulfonamide drugs, if any, is preferable, so that in vitro studies of the susceptibility of a patient's organism to the different sulfonamides would be helpful in selecting a drug.

Heparin was added on the theory that it would inhibit fibrin formation¹⁰ and so "restrict the nidus and culture medium for bacterial growth, prevent embolism from the freeing of fresh thrombus, and check the growth of the vegetations so that proliferating fibroblasts may fill in the areas thus limited"⁷

According to the method of Kelson and White, after one week of sulfapyridine therapy, heparin was administered intravenously for 14 days, a venous clotting time of approximately one hour being maintained. Sulfapyridine was given continuously for a total of four weeks.

That heparin actually prevents the deposition of fibrin and platelets on a damaged valve has not been proved, although it has been effective in preventing thrombosis in experimental animals. However prolonged the bleeding time, it is probable that thrombus formation continues, although at decreased speed. A case treated with heparin alone died on the fourteenth day of treatment. Microscopically the valve differed in no way from those seen in untreated cases. Bacterial vegetations were covered with fibrin thrombus, much of the fibrin appearing to be of recent deposition.¹¹

Success of the combined treatment would depend on several concurrent circumstances: (1) a bacteria susceptible, when accessible, to the drug employed, and not present in overwhelming numbers and virulence, (2) a sufficiently active reparative fibrosis, (3) concentrations of the inaccessible bacteria within thrombi or valve substance not too large to withstand the leukocytic and fibroblastic activity, (4) foci of inaccessible bacteria limited to areas small enough to be wiped out by leukocytes and fibrosis during the period of treatment.

Theoretically, an ideal combination of these circumstances should lead to a cure.

Clinically, it would seem that when sulfanilamide or sulfapyridine is introduced into the body the accessible organisms, if susceptible, are rather quickly inhibited. This produces objective or subjective improvement (decrease in toxicity, lowering of temperature, sterilizing of blood cultures) for periods of a few days to weeks depending upon the virulence of the organisms, the number of foci, and the speed of multiplication.

However, if the inaccessible organisms not reached by the drug are not destroyed by the defensive and reparative processes within the valve substance, they continue to multiply, with gradual resumption of previous clinical signs and symptoms. In addition to the effect of these hidden and protected organisms, the streptococcus may develop an immunity to the action of the drug, so that even larger doses become ineffectual.

The following case was treated with heparin, sulfapyridine, and sulfathiazole.

CASE REPORT

White male, aged 44 years, entered the medical service July 9, 1941, with a six months' fever, joint pains, and loss of strength

Past history was non-contributory, except for scarlet fever at fourteen

In January, 1941, he had "influenza" for four days, from which he apparently recovered. Two weeks later, he had pain and swelling of the left jaw for five days. During the month of February, he grew progressively weaker and had aching joints. A blood culture on February 26 was positive for a streptococcus, and he was given sulfapyridine until May 1. Although weak, he felt well, and returned to work. In June, he felt worse and took to bed. He was given sulfapyridine for one month, but blood culture remained positive. He returned to work for 10 days and then entered the hospital.

He was well developed, ambulatory, and did not appear acutely ill. There was no evidence of petechiae in the skin, mucous membranes, or fundi. Teeth were in good condition with no marginal gum infection. The throat was clean. Heart was normal in size, with a fairly loud systolic murmur in the mitral area. No diastolic murmur was heard, and the rhythm was regular. Liver and spleen were not palpable.

Course. Blood cultures were positive for *Streptococcus viridans* on July 9, 13, 16. On July 19, sulfathiazole was begun, and continued to August 20. Blood concentrations of free sulfathiazole ranged between 5 and 7.9 mg per cent. Blood cultures: July 24, no growth; July 30, no growth; August 5, heavy growth; August 12, small growth; August 20, good growth.

Ten days after starting sulfathiazole, following a chill and rise in temperature to 103°, an erythematous maculo-papular eruption appeared over the entire body and persisted. His temperature swung between 100° and 104°. Despite these toxic drug manifestations, sulfathiazole was continued three weeks longer. On its discontinuance the temperature immediately dropped to normal and the dermatitis quickly disappeared. For 19 days thereafter, he was afebrile, although a blood culture during this period (September 4) showed a heavy growth of *Streptococcus viridans*.

On August 28, sulfapyridine was begun and continued until December 8. The level of free sulfapyridine ranged between 4.5 and 5 mg per cent. Repeated blood cultures were positive throughout.

There was no change in his febrile state. On several occasions he showed petechiae, and twice had symptoms of splenic infarction. Although blood cultures during September and October showed abundant growth, it was decided to administer heparin intravenously. His general condition at this time was good. Coagulation time, according to the method of Lee and White, was 3¼ minutes.

Heparin was begun on October 28 and continued uninterruptedly for 14 days. Because of the frequent reports of cerebral hemorrhages during the administration of heparin, it was decided not to prolong the clotting time to one hour, but to maintain it between 20 and 30 minutes. Coagulation time was determined every six hours, and exhibited moderate fluctuations. On a few occasions the coagulation time rose to 35 and 40 minutes, requiring alterations in the speed of heparin flow. A total of 660 cc of heparin was given. The average clotting time over the entire period was 23 minutes. There were no evidences of bleeding or infarction during this procedure.

There was no change in his clinical condition. Fever remained active. Blood culture, after one week of heparin, showed 45 colonies per cc of blood, after two weeks, 40 colonies per cc of blood. On November 25, two weeks later, he had a cerebral embolus. From this time on, his condition grew steadily worse, and he expired on December 26.

Autopsy was performed 30 minutes after death. The mitral valve showed a few granulations and rather easily detached, small, reddish, fungoid growths. The aortic valve was involved with massive amounts of similar granular, friable, reddish growths,

not only on the cusps but also in the aorta adjacent to the aortic valve and beneath the aortic valve on the surface of the left ventricle

Microscopically, sections through the valve and vegetations showed large areas of necrosis and masses of densely packed, gram positive cocci

To date, 55 cases treated with heparin and sulfapyridine have been reported ^{7, 12, 13, 14, 15, 16, 17, 18, 19, 20}

Following their original series of seven cases, with "striking improvement" in three, Kelson and White treated 19 more, 18 of which were failures. Since the appearance of their paper others have appeared, reporting three recoveries and 26 failures

An analysis of the seven cases benefiting from combined therapy discloses four that may be regarded as cured. One of these developed acute rheumatic fever and congestive failure, dying six months after treatment ⁷. The heart at autopsy showed complete healing of the vegetations. The second case was well 18 months after treatment. However, the author states "an analysis of the therapy in this case suggests the probability that the success of the treatment would have occurred without the use of heparin. The febrile course was interrupted on the first day following commencement of sulfapyridine. The first negative blood culture was reported prior to the use of heparin" ¹⁶. The third case, ⁷ at the time reported, had been well 26 weeks after treatment, and the fourth had been well for six months ¹⁷.

The fifth had "still remained free of evidence of the disease four weeks after stopping treatment" ⁷. However, conclusions cannot be drawn after such a brief interval since Capps states, "A considerable number of cases who become apparently well for months, or even a year or two, undergo a relapse with fresh bacteremia" ²¹.

In the sixth case, the diagnosis was not proved ¹⁸. There are no published details available for the seventh case which has been reported as cured ¹⁹. These cases of cure or improvement may well have been due to the sulfapyridine employed, since 12 from a total of 198 cases treated with sulfanilamide or sulfapyridine alone have been reported as cured ¹⁹.

Of 22 heparin-treated cases where reported details are available, eight died of cerebral hemorrhages during the administration of heparin.

Discouraging as are the results of treatment by the sulfonamides, with apparently specific cures few and far between, they appear no more discouraging than those of the sulfapyridine-heparin combination. It would seem fair to conclude that heparin offers no advantages and has distinctly harmful potentialities. These facts, coupled with the expense and the difficulty of the control and management of the treatment, make very questionable the value of its further employment in the treatment of subacute bacterial endocarditis.

BIBLIOGRAPHY

- 1 HEYMAN, JACOB. Subacute bacterial endocarditis successfully treated with sulfanilamide. Report of well established case 18 months after recovery, *Jr Am Med Assoc*, 1940, **CXIV**, 2373.
- 2 CHRISTIE, AMOS. Subacute bacterial endocarditis apparently cured with sulfanilamide, *Jr Am Med Assoc*, 1940, **CXV**, 1357.
- 3 MAJOR, RALPH H. The effect of sulphanilamide compounds on endocarditis, *Am Jr Med Sci*, 1940, **CXCIX**, 759.

- 4 STEELE, HUGH H The effect of sulfanilamide on the length of life of patients with subacute bacterial endocarditis, *New England Jr Med*, 1940, ccxxii, 1067
- 5 SPINK, WESLEY W, and CRAGO, F HUGHS Evaluation of sulfanilamide in the treatment of patients with subacute bacterial endocarditis, *Arch Int Med*, 1939, lxiv, 228
- 6 KINELL, JACK and ERNSTENE, A CARLTON Subacute bacterial endocarditis—five cases treated unsuccessfully with sulfapyridine, *Cleveland Clin Quart*, 1940, vii, 83
- 7 KELSON, S R, and WHITE, P D A new method of treatment of subacute bacterial endocarditis, using sulfapyridine and heparin in combination, preliminary report, *Jr Am Med Assoc*, 1939, cxiii, 1700
- 8 SWAIN, R H A Strain variations in the resistance of *Streptococcus viridans* to sulfonamide compounds, *British Med Jr*, 1940, i, 722
- 9 DUNCAN, C N, and FAULKNER, J M Penetration of blood clot by sulfanilamide, sulfapyridine, sulfathiazole, and sulfamethylthiazole, *Am Jr Med Sci*, 1940, cc, 492
- 10 FRIEDMAN, MEYER, HAMBURGER, W, and KATZ, L W Use of heparin in subacute bacterial endocarditis a preliminary report, *Jr Am Med Assoc*, 1939, cxiii, 702
- 11 FLETCHER, C M Failure of heparin in subacute bacterial endocarditis, *Lancet*, 1941, i, 444
- 12 WITTS, L J Heparin in subacute bacterial endocarditis, *Brit Med Jr*, 1940, i, 484
- 13 DOCKERAY, GERALD C, and KAWERAU, EINHART Heparin in subacute bacterial endocarditis, *Brit Med Jr*, 1940, ii, 703
- 14 MILLER, EDGAR R Use of heparin in treating a case of subacute bacterial endocarditis with patent ductus arteriosus, *Delaware State Med Jr*, 1940, xii, 177
- 15 FLETCHER, C M Subacute bacterial endocarditis treated with sulfapyridine and heparin, *Lancet*, Oct 26, 1940
- 16 DRUCKMAN, J S A case of subacute bacterial endocarditis with apparent cure, *Jr Am Med Assoc*, 1941, cxvii, 101
- 17 PETCH, C P Heparin and sulfapyridine in subacute bacterial endocarditis, *Lancet*, 1940, ii, 637
- 18 WEEKS, DEF Case of subacute bacterial endocarditis treated with heparin and sulfapyridine, *Jr Maine Med Assoc*, 1940, xaxi, 200
- 19 LICHTMAN, S S, and BIERMAN, WILLIAM The treatment of subacute bacterial endocarditis present status, *Jr Am Med Assoc*, 1941, cxvi, 286
- 20 SEVITT, S Treatment of subacute bacterial endocarditis with heparin and sulfapyridine, *Lancet*, 1941, i, 443
- 21 CAPPS, J A Subacute bacterial endocarditis, due to *Streptococcus viridans*, with special reference to prognosis, *ANN IN MED*, 1939, xiii, 280

UVEOPAROTITIS; A REPORT OF TWO CASES '

By WILLIAM HARBIN, JR, M D, F A C P, and THOMAS S HARBIN, B S,
Rome, Georgia

DURING recent years there has been a decided increase in the number of reported cases of uveoparotitis. A rather comprehensive review of the literature reveals that approximately 100 such cases have been reported, less than 20 of which come from America and the remainder from foreign countries, chiefly Scandinavia, England and Germany. The rarity of this syndrome warrants the mention of additional cases and the careful scrutiny of these entities with regard to etiology.

* Received for publication May 28, 1940

Parotitis uveitis, and a low grade fever are the essential features of this condition. Prodromal symptoms, lasting for several weeks or months, include general malaise, drowsiness, weakness, nausea, vomiting, and loss of weight. Other signs and symptoms which are often encountered during the course of the illness include paralysis of the cranial nerve (particularly the seventh), a slightly elevated, discrete, erythematous rash occurring chiefly on the extensor surfaces of the forearms and legs, dryness of the mouth, various aching pains, polyuria and night sweats. Occasionally the submaxillary, sublingual or lacrimal glands are enlarged and also the cervical lymph glands.

The disease runs a chronic course, the symptoms lasting for months or for several years, and one of its features is the irregularity in the onset of symptoms. It may occur at any age, but is more common in the second and third decades and is slightly more prevalent in females. The morbidity is high whereas the mortality is low, only five deaths having been recorded.

The parotid glands are usually involved early in the course of the disease. They become enlarged and hard, and although not painful may be slightly tender. The glands are not adherent to the skin and never suppurate. The swelling, which is usually bilateral, lasts for months or years.

Inflammation in the uveal tract is present in all cases of uveoparotitis. The first ocular symptom is usually dimness of vision, associated with circumscribed corneal injection and narrowing of the palpebral fissures. Occasionally there is pain. Although in the beginning the involvement may be unilateral, bilateral uveitis usually follows. The pupils are often sluggish, dilated, or irregular, with a tendency to develop posterior synechiae. The other important eye findings which may be observed are fatty deposits on the posterior surface of the cornea, nodules in the iris, vitreous opacities, keratitis, optic neuritis and atrophy.

Reference is made to several excellent reviews of the literature on this subject, and no attempt will be made to duplicate such reports. The first description of this syndrome was given by Heerfordt¹ in 1909. Garland and Thompson,² Savin,³ and Folger⁴ have made comprehensive and critical surveys of the literature on this subject, while Levin⁵ has reported in detail on the neurological aspect of the syndrome.

CASE REPORTS

Case 1 A 35 year old negro male came to the Harbin Hospital on May 17, 1937, with a chief complaint of aching pain throughout the chest and abdomen associated with nausea and vomiting. On several occasions during the previous year he had had severe gastrointestinal "upsets" associated with aching pain in the chest and abdomen. His temperature had been moderately elevated for several days with these attacks. His employer stated that at times he was rather drowsy and acted as if he might be drugged, enough so that it was questionable whether he should continue his work as a chauffeur.

About three years prior to the time he was first seen he had consulted Dr. George B. Smith (ophthalmologist) because of dimness of vision, and in July 1934 a diagnosis of uveitis was made.

The patient's first wife had died of pulmonary tuberculosis in 1930, and one child by this wife was confined to a tuberculosis sanatorium at the time of his examination. His second wife was healthy. He used tobacco excessively and during each winter had frequent head colds with a slight cough. At the age of 20 he had had a gonorrheal infection, but no history of a chancre could be obtained.

Physical examination revealed a well developed, well nourished negro male not acutely sick. The lacrimal glands were swollen, considerable bilateral circumcorneal injection was present, the pupils reacted sluggishly to light and were irregular. Moderate dental caries and pyorrhea were present. Both parotid glands were enlarged, firm, smooth and slightly tender without any fixation of the skin. Upon being questioned, the patient stated that his wife had commented upon the appearance of each side of his face several times in the four or five months prior to the time of his examination. The submaxillary glands were not enlarged but several cervical lymph glands were palpable. Physical examination of the heart and lungs was not remarkable. The blood pressure was 120 mm Hg systolic and 78 mm diastolic. There was slight tenderness in the region of his umbilicus, otherwise his abdomen was negative. The biceps and patellar reflexes were normal. Dr Smith reported that the uveitis had improved, that no posterior synechiae were present, and that his visual acuity was normal.

The first specimen of urine examined contained a small amount of albumin and a moderate amount of pus. Urinalyses at later dates, after the administration of urinary antiseptics, were negative. The blood findings were as follows: hemoglobin 92 per cent (Sahli), red blood cells 4,010,000, leukocytes 9,650, polymorphonuclears 60 per cent, eosinophiles 2 per cent, mononuclears 3 per cent, small lymphocytes 31 per cent, large lymphocytes 4 per cent. The blood Wassermann and blood Kahn reactions were negative. No malarial parasites were found. Examination of the spinal fluid revealed a cell count of 6, very small amounts of globulin and sugar, and a negative Kahn reaction. Colloidal gold showed no color change. A chest roentgenogram revealed normal lung fields and a cardiac outline within normal limits. The injection intradermally of 0.01 mg of Old Tuberculin gave a positive reaction.

On June 15, 1937, the patient stated that he felt much better, that his drowsiness was less, and that no attacks of vomiting and abdominal pain had occurred. The physical findings on that date were unchanged. By request he returned on March 28, 1938 for a routine examination. Since last seen he had had two "slight attacks" of fever and general aching in the chest and abdomen, accompanied by vomiting. He stated that the enlargement of the parotid glands had varied in size, and they were found to be definitely smaller than at the time of his first examination. His sight had been good, and only a slight ciliary injection was noticed. He continued to be drowsy at times. The examination of his urine was negative.

He was seen again on June 24, 1938, at which time he had no complaint. The swelling of the lacrimal glands had disappeared and the eyes were grossly normal. The parotid glands continued to be slightly enlarged, chiefly on the right side. He had no nausea, vomiting, or aching pains, and his urine was negative. On March 2, 1940, he stated that his general health had been good since June of 1938. Very slight enlargement of both parotid glands was present, and the ophthalmologist reported normal eye findings.

This patient was not observed when he first had symptoms probably associated with uveoparotitis, as he reported dimness of vision almost three years before he was examined. As might be expected, in view of the intellect of the patient, the history regarding the duration of his general symptoms was vague. At no time did he take his condition seriously, and he was examined at the insistence of his employer.

Case 2 A 21 year old white American female came to the Harbin Hospital March 26, 1938 with a chief complaint of blurred vision in the right eye. For several days her right eye had been red, and the visual disturbance had been noticed for about two weeks. The patient stated that she had been a nervous person all her life but more so recently. At the age of 13 she was taken out of school for one year upon the advice of her physician because of a "rapid heart rate." Several years later she was told by another physician that she had a "leaking heart." It was not possible to elicit a history of any other cardiac disturbance. Two years prior to the time of her

examination she had had slight contact with a person who had active pulmonary tuberculosis. Otherwise her past history was not remarkable, and a review of her systems was non-contributory.

Physical examination revealed a poorly nourished, fairly well developed woman, 5 feet 4½ inches tall, weighing 108 pounds. Her temperature was 99.2° F. The pupils were equal, regular, and reacted to light and accommodation. A slight epiorbital injection was present in the right eye. The mouth was not remarkable, with the exception of slight dental caries. The parotid and submaxillary glands were not enlarged, neither were the cervical lymph glands. Examination of the heart and lungs did not reveal any positive findings, and the blood pressure was 118 mm Hg systolic and 82 mm diastolic. The abdomen was negative and the reflexes physiological. The blood count was as follows: hemoglobin 75 per cent (Sahli), red blood cells 3,760,000, leukocytes 7,500, polymorphonuclears 55 per cent, monocytes 2 per cent, eosinophiles 3 per cent, small lymphocytes 34 per cent, large lymphocytes 6 per cent. The urine was found to be normal, and the blood Kahn test was negative. A roentgenogram of her chest revealed normal lung fields and a cardiac outline within normal limits. A tuberculin test using 0.005 mg of purified protein derivative tuberculin was negative.

During the following weeks her temperature ranged from normal to 100.5° F, and on April 22, 1938, a slightly elevated macular erythematous rash appeared on the arms, lower legs and feet. On April 29, 1938, an ophthalmological examination was made by Dr. F. P. Calhoun, and his report was as follows: "Vision right and left 15/15. The near points of accommodation were 10 cm, there was no muscle imbalance and the intraocular tension was normal. The right eye showed a slight periorbital injection, and the left eye showed a moderate periorbital injection. Dilating the pupils for a fundus and slit lamp examination, many cells were found on the posterior surface of the right cornea, none was found on the left cornea although the aqueous beam was cloudy. With the ophthalmoscope vitreous cells were seen in the right eye but no other pathology, and the fundus of the left eye was normal. Diagnosis, bilateral cyclitis."

When the patient was seen on May 5, 1938, both submaxillary glands were enlarged and slightly tender. No enlargement of the parotid glands could be detected, the skin rash was still present and had not changed. After having been on a high caloric diet for several weeks she had gained about two pounds in weight. At that time she complained of a dry sensation in her mouth. On May 12, 1938 she stated that she had been nauseated for 18 hours and had vomited several times. During the few days preceding that date she had had various aching pains throughout her body which at times were severe. She continued to have a slight elevation in temperature, and her skin rash was fading. The ophthalmologist reported that her eyes were beginning to improve.

During the next few months she improved in general, the skin rash disappeared, her temperature was lower, and her eyes approached normal. The precipitates on the posterior surface of the cornea disappeared. On September 9, 1938, the left submaxillary salivary gland was not palpable, but the right continued to be slightly enlarged. By November 8, 1938, the patient was feeling very well and weighed 122 pounds. About one year later, in December of 1939, she complained that her vision was not quite normal, although it was fairly good. Dr. Calhoun reported as follows: "the vision was slightly improved and the slit lamp and fundus examinations were normal." Her general condition at that time was excellent.

During the early course of her illness therapeutic measures were instituted to improve her general condition. She was on a high caloric diet, ferrous sulphate was administered for the secondary anemia, she was in bed for several weeks, and efforts were made to relieve her nausea, aches and pains. At the suggestion of the ophthalmologist her pupils were dilated with atropine for several months until the cyclitis had completely subsided.

COMMENT

The first case presents typical findings of uveoparotitis. It is of interest to note that this patient had had much contact with active pulmonary tuberculosis and that his tuberculin test was positive. However, he did not have any clinical or roentgen-ray evidence of pulmonary tuberculosis. He improved considerably during the first few months he was under observation and after almost three years his condition continued to be good and his vision normal. The parotid glands were known to have been enlarged for about three years and were still enlarged at the time of his last examination in March 1940. No serological evidence of lues could be obtained.

In the second case the following characteristic findings of the uveoparotid syndrome are present: fever, bilateral cyclitis, skin rash, dryness of the mouth, nausea, vomiting, aching pains, and enlargement of the submaxillary glands. The fact that no enlargement of the parotid glands was detected makes a diagnosis of uveoparotitis questionable. In quite a number of the cases reported in the literature there was enlargement of the submaxillary or sublingual glands in addition to parotid enlargement. The authors feel that the evidence presented favors the diagnosis of uveoparotitis and would like to suggest that this syndrome may occur with enlargement of one of the salivary glands other than the parotids. Of interest is the fact that epidemic parotitis is known to occur with involvement of the submaxillary or sublingual glands, without any enlargement of the parotids.

The recognition of this condition is important from the point of view of prognosis and treatment. As a rule this disease is a self-limited one and treatment should be directed chiefly toward improvement of the patient's general condition, the alleviation of distressing symptoms, prevention of complications, and reassurance as to the probable outcome. One important therapeutic measure is the maintenance of mydriasis in an effort to avoid the formation of posterior synechia with permanent impairment of vision. Failing to diagnose this syndrome correctly may result in a faulty prognosis being given to its various manifestations, and may lead to unjustifiable treatment.

It has been established beyond any doubt that this syndrome is a well defined clinical entity. There is, however, a great diversity of opinion as to the etiology of this disease and a variety of causes have been suggested by authors who have reported cases. It is frequently referred to as uveoparotid tuberculosis, and in several cases evidence of tuberculosis has been obtained. There are those who believe that all such cases are tuberculous in origin but no sound proof has been offered to substantiate this theory. In the majority of cases tuberculosis has not been demonstrated, and the tuberculin reactions have been negative. Referring to this disease, Cohen and Rabinowitz⁶ made the following statement: "the tuberculous patient is tuberculin sensitive except under conditions of massive tuberculous infection, but it must be conceded that the patients in this series had no massive infection, if at all infected, it was mildly, and yet the tuberculin reactions were negative in the majority of instances, in the cases in which the tubercle bacillus was demonstrated, the reaction was positive." It has been suggested by Lewis, Raines and Stewart⁷ that this disease may not be due to any one specific infection but that it is a manifestation of local tissue hypersensitivity to any one of a variety of allergens, and that although tuberculin may

often be the allergen responsible, it is unwise to regard all cases of uveoparotitis as tuberculous. At the present time this appears to be the logical explanation of the cause of uveoparotitis. That it may be due to an organism which has not yet been identified must be considered. If the latter should be the case, this unknown organism apparently produces a low grade infection in a sensitized individual, the course of which is chronic with a spontaneous termination.

As it was not possible to demonstrate any primary tuberculous focus in the first case one cannot say that it was caused by tuberculosis, even though there was much contact with active pulmonary tuberculosis and the tuberculin test was positive. It must be remembered, however, that an infection of this type might have been present but not detected. In the second case the tuberculin reaction was negative, no causative agent was found, and its etiology remains unknown.

SUMMARY AND CONCLUSIONS

- 1 The findings in a typical case of uveoparotitis are described.
- 2 The possibility of this syndrome's occurring with involvement of one of the salivary glands other than the parotids is suggested and such a case is reported.
- 3 The importance of the recognition of this clinical entity is stressed.
- 4 The need of further knowledge of the etiology of uveoparotitis is pointed out. It is suggested that the syndrome may arise from hypersensitivity to a number of allergens.

BIBLIOGRAPHY

- 1 HEERFORDT, C. F. Über eine "Febris Uveoparotides subchronica" an der Glandula Parotis und der Uvea des Auges lokalisiert und häufig mit Paresen cerebrospinaler Nerven kompliziert, *Arch f Ophth*, 1909, lxx, 254.
- 2 GARLAND, H. G., and THOMPSON, J. G. Uveo-parotid tuberculosis, *Quart Jr Med*, 1933, ii, 157.
- 3 SAVIN, L. H. An analysis of the signs and symptoms of sixty-six published cases of the uveoparotid syndrome, *Trans Ophth Soc United Kingdom*, 1934, liv, 549.
- 4 FOLGER, H. P. Uveoparotitis (Heerfordt), *Arch Ophth*, 1936, lv, 1098.
- 5 LEVIN, P. M. The neurological aspect of uveo-parotid fever, *Jr Nerv and Ment Dis*, 1935, lxxvi, 176.
- 6 COHEN, S. J., and RABINOWITZ, M. A. Uveoparotitis, *Jr Am Med Assoc*, 1935, cv, 496.
- 7 LEWIS, G. E., RAINES, ROBERT, and STEWART, D. S. Uveoparotitis, *Lancet*, 1936, ii, 1204.

EDITORIAL

VACCINATION AGAINST RICKETTSIAL INFECTIONS

Two types of rickettsial infections are associated with so high a mortality and (at least, at some times) so high a morbidity that effective preventive measures are of great practical importance. These are epidemic ("Old World") typhus fever, and the Rocky Mountain spotted fever.

Spotted fever is conveyed to man by the bite of the wood tick. Man does not constitute an essential link in the life cycle of the infection. The natural reservoir of the virus is the tick, in which it passes from one generation to the next through the egg, and probably also various wild mammals on which the ticks feed. Man is only accidentally and incidentally infected.

The mortality of spotted fever varies greatly depending upon the virulence of the strain of virus involved and the locality in which it occurs. In Western Montana it may be 75 per cent or more, whereas in most regions, including the southeastern states, it is usually given as from 10 to 20 per cent. The incidence of the disease in the general population is so low that wide spread vaccination, if feasible, would hardly appear indicated. In those occupational groups, however, whose work exposes them to the bites of infected ticks, morbidity and mortality may both be high and any available means of protection most important. This applies, for example, to sheep herders, and to laboratory workers, particularly those handling infected ticks.

The theoretical possibility of securing protection by vaccination was indicated by the fact that recovery from natural infection was followed by a substantial degree of immunity. The U. S. Public Health Service, since the report of Spencer and Parker (1925), has employed a vaccine made by grinding up infected ticks in phenol-formalinized salt solution. Parker¹ has recently reported the results obtained over a period of 15 years. By giving two doses of 2 c.c. each, representing in all the virus obtained from five ticks, a substantial degree of protection was obtained. This was only temporary, however, and immunization had to be repeated annually. Reactions to the vaccine were usually mild, and no serious accidents were reported. Protection from the more virulent strains was only relative as a rule, but in the case of the milder types it was fairly complete. Thus during the period of 15 years, in an area of Western Montana in which the incidence of the disease was low but the mortality high, 51 cases of infection occurred in non-vaccinated individuals, with a mortality of 42, or 82 per cent; there were 37 cases in vaccinated adults, with a mortality of 3, or 8 per cent. Among their laboratory staff, 19 cases occurred in vaccinated individuals with one death, whereas 8 cases in unvaccinated individuals were all fatal. In a dis-

¹ PARKER, R. P. Rocky Mountain spotted fever. Results of fifteen years prophylactic vaccination. *Am. Jr. Trop. Med.*, 1941, *xxi*, 369-384.

strict in southern Idaho, in which the disease incidence was high but the mortality low, one case only occurred among 193 vaccinated, but there were 22 cases among 364 controls—a twelve fold difference. The course of the disease was milder and shorter in vaccinated cases.

Vaccines against tick-borne rickettsial strains in other localities (South Africa, South America) have been prepared in a similar manner, and have afforded protection in animal experiments. Thus far no extensive trials in man have been reported.

Typhus fever appears in two forms: the epidemic, or "old world" typhus, and endemic or murine typhus. These types are similar from the immunological standpoint, although they show quantitative differences, but they differ in their virulence, and in their epidemiology. Epidemic typhus is naturally a disease of man. Man constitutes the reservoir of the virus, and it is conveyed by the human body louse.

Endemic typhus is naturally a disease of rats which constitute the reservoir of the virus. It is conveyed like plague, by the rat flea (and from rat to rat also by the rat louse). It occurs sporadically in man, wherever man comes into close contact with these rodents and is exposed to the bites of infected fleas. It is widely distributed in seaports in the warmer climates, and is fairly common in the southeastern United States.

The virus of endemic typhus is more virulent for rodents, but in man causes a milder type of infection than does epidemic typhus, with a mortality in this country of less than 1 per cent, according to Dyer. Under such conditions, immunization on a large scale would hardly be worth the effort, although it might be desirable for those most intimately exposed.²

Epidemic typhus, on the other hand, once started, attacks large numbers of individuals and has a mortality rate varying from about 10 per cent to 70 per cent in different epidemics. In time of war, famine or other communal disasters, when epidemics of typhus are prone to occur, a general immunization of the population would manifestly be of the utmost value.

Recovery from typhus is followed by a substantial degree of resistance of considerable duration, although the occasional occurrence of second attacks indicates that it is not complete or permanent. Furthermore, for a short period after recovery protective substances can be detected in the serum. These facts indicate that theoretically at least, protection by vaccination should be possible.

The earlier attempts utilized living vaccines of murine typhus—of low virulence to man. Blanc attempted to attenuate the virus still further by suspending it in ox bile. Laigret made a suspension of infected guinea pig brain tissue in egg yolk, desiccated this, and later resuspended it in olive oil. Such vaccines were extensively used in the French colonies in northern Africa where it is reported over a million individuals were vaccinated. It is difficult to evaluate the results obtained. Laigret et al.³ reported in detail

² DYER, R. E. The control of typhus fever, *Am. Jr. Trop. Med.*, 1941, **xvi**, 163-184.

³ LAIGRET, J., et al. La vaccination contre le typhus exanthématique par la vaccine enrobe de l'institut Pasteur de Tunis, *Arch. Inst. Pasteur de Tunis*, 1937, **xxvi**, 454-623.

regarding a group of 32,481 vaccinated individuals in a population of 212,000. They reported five "certain" and eight "suspected" cases of murine typhus—all mild—developing as a direct result of the vaccination. However, vaccine was given extensively to groups in which an epidemic of typhus was developing and the disease appeared in an appreciable number of cases within a short time (less than two weeks) after vaccination. In all such groups, the epidemic subsided within three weeks. The incidence of typhus developing one month or more after vaccination was less than one per thousand, and all such cases recovered. The total number of cases in the entire population of 212,000 was 2,634, with 298 deaths. It appears, therefore, that the vaccine conferred a substantial degree of immunity for a period of at least one to two years. The use of a living vaccine, however, cannot be regarded as desirable, or under ordinary conditions as justifiable, in view of the risk involved, both to the individual inoculated and to the community at large.

Many attempts have been made to use killed vaccine. In one experiment, an epidemic typhus vaccine was prepared by grinding up the spleens of mice infected with the virus in carbolyzed salt solution. The mice were infected with the virus as from 10 to 20 per cent of a suspension of rickettsiae, they were then killed, and the spleens were ground up. The general population is so low that the use of such a vaccine would hardly appear indicated. In another experiment, the vaccine apparently secured a substantial degree of protection. However, as it required about 100 lice to produce infection in an individual, the procedure is obviously useless for the general population. This applies, for example, to

Zinsser first secured the virus in abundance from rats which had been poisoned with the virus. The exudate was suspended in formalin. Protection by vaccination was indicated by the fact that mice vaccinated with the vaccine were protected. The vaccine was followed by a series of experiments in which the vaccine was given to over 2,000 human cases of typhus. Since the data were given as to the degree of protection obtained, it is not clear whether the vaccine was made by suspending the lungs of rats, in which a rickettsial pneumonia had been produced by intranasal inoculation. With this vaccine he obtained protection in guinea pigs and in a few human volunteers. Additionally, five amounts of murine vaccine protect animals from epidemic typhus as well as from endemic typhus, although it gives quantitatively more effective protection from the latter type.

Attempts have also been made to utilize tissue culture suspensions as a source of vaccine. Zinsser⁵ used minced 10 day chick embryos on serum agar. Cox⁶ inoculated the yolk sac of developing chick embryos by direct injection of rickettsial suspensions. By both methods an abundant growth of rickettsiae can be obtained. Technically, Cox's method promises to be

⁴ CASTANEDA, M. R. Experimental pneumonia produced by typhus rickettsiae, *Am J Path*, 1939, 44, 467-475.

⁵ ZINSSER, H., PLOTZ, H., and ENDERS, J. F. Mass production of vaccine against typhus fever of the European type, *Science*, 1940, 81, 51-52.

⁶ COX, H. R., and BEIL, E. J. Epidemic and endemic typhus protective value for guinea pigs of vaccines prepared from infected tissues of the developing chick embryo, *Pub Health Rep*, 1940, 15, 110-115.

the most satisfactory By such culture methods it is possible to secure the virus of epidemic typhus in abundance, as well as murine typhus This one would expect to be quantitatively more effective than the murine vaccine in man as a protection from the epidemic disease With this vaccine Cox was able to protect guinea pigs, but so far no reports have appeared regarding its use in man

Thus far none of these killed vaccines has been used in man, under epidemic conditions The present war has created conditions in eastern Europe which seem ideal for the development of extensive epidemics of typhus We may hope that this opportunity can be utilized to test the efficacy of these vaccines on a large scale Thus far one may say only that the prospects are promising, but the procedure is still in the experimental stage The value of the spotted fever vaccine for those who are exposed to the infection may be regarded as established, although there is still uncertainty as to the degree and duration of the protection

P W C

ERRATUM

On page 168, ANNALS OF INTERNAL MEDICINE, January, 1942, sixth line from foot should read

The roentgen-ray examination of the kidneys showed a large calculus almost filling

REVIEWS

Radiologic Physics By CHARLES WEYL, S REID WARREN, JR, and DALLEY B O'NEILL 459 pages, 24 X 16 cm Charles C Thomas, Springfield, Illinois 1941 Price, \$5 50

This volume is divided into two parts (1) the theory and practice of electrical engineering as applied to radiological apparatus, (2) the theory and application of radiation physics with reference to roentgen-ray diagnosis and roentgen- and gamma-ray therapy

The authors have produced a clear and well integrated development of the fundamental theories underlying radiation technic starting with elementary electricity and mechanics and carrying the reader through an analysis of electric circuits, electrical instruments and apparatus, and electronics to a consideration of the theory of radiant energy, roentgen-rays and matter, and radioactivity and nuclear physics

The technical and teaching experience of the authors is reflected in the excellent treatment of the practical aspects of radiation technics, the measurement and control of roentgen-rays and gamma-rays, and variations of exposure factors The mathematics necessary to the formation of accurate concepts of the various phenomena is developed along with the theory The simplicity of presentation and addition of a good appendix on the elements of algebra, trigonometry, and calculus permit a ready grasp of the subject by those without advanced training and are of particular value for the clinician who has been too long away from mathematical problems

An exception to the thorough treatment of the different subjects prevalent in most of the book exists in the chapter on electromedical apparatus in which some sections, as for example those dealing with infra red and ultra violet radiation and electrocardiography, are so brief as to be hardly worth inclusion In view of its possibilities for deep therapy more might be written of the van de Graff high voltage type of roentgen-ray generator Also, it would be useful to have a more complete listing of the new artificially radioactive substances included in any future editions

Of especial value to active workers in this field are the tables of useful data and the many helpful charts, graphs and diagrams given throughout the book Each chapter is followed by an adequate and up-to-date list of special and general references Last but not least is the section on safeguards against roentgen-ray burn and shock

R H O

Applied Pharmacology By HUGH ALISTER MCGUIGAN, PH D, M D, F A C P 914 pages, 25 X 17 cm The C V Mosby Co, St Louis 1940 Price, \$9 00

This text is a comprehensive treatise dealing with the application of pharmacological information to therapeutics The approach to the subject matter is one representing pharmacodynamics as the scientific basis of the clinical use of drugs

The book is divided into 86 sections Drugs having related pharmacological action are classed together A number of interesting and, for pharmacology texts, novel sections have been included Thus, one finds chapters on barometric pressure, incidental conditions of the air, the reticulo-endothelial system, water, odors and the pharmacology of ganglia The usual subdivisions of this subject are given in detail Twenty pages are devoted to the principles of prescription writing A well selected bibliography is appended to each section

From the standpoint of the teacher of pharmacology the volume is to be recommended Students will find the information clearly presented and well documented with tables, illustrations and structural formulas The therapeutic approach also will appeal to most students

The physician will find this volume a valuable reference work although the treatment of some of the newer drugs is extraordinarily brief. For example, only four pages have been devoted to the sulfonamide drugs. On the other hand some sections, for example, anesthesia, have been given in great detail. The discussion on theories of anesthesia is excellent.

The author is to be commended for his modern treatment of the section on prescription writing. He recommends the use of English instead of Latin and points out the therapeutic advantage of simple, one-drug medication.

The typography and composition of the book are of the usual creditable quality of the publisher.

C J C

Headache and Head Pains By WALTON FOREST DUTTON, M D 301 pages, 23.5 × 15.5 cm F A Davis Co, Philadelphia 1939 Price, \$4.50

The author lists in alphabetical order over 200 conditions associated with headache and head pain. He very briefly discusses their etiology, symptomatology, and treatment. The material is not arranged in a manner favorable for use as a differential diagnosis. A considerable portion of the text is devoted to prescriptions, which are in many instances sedatives and reappear with slight variations throughout the book. Under treatment the author also includes prescriptions directed toward the specific disease. Head pain per se is discussed only briefly in the introduction. He has not seen fit to become involved with the severe type of protracted headache of vague etiology which so frequently baffles the physician. The book is not recommended.

E F C

The Principal Nervous Pathways By ANDREW THEODORE RASMUSSEN, PH D 73 pages, 28.5 × 21.5 cm The Macmillan Company, New York 2nd edition, 1941 Price, \$2.50

This book was originally published in 1932 and has since been used for medical teaching. The general construction of the second edition is unchanged, consisting of the same number of schemas with accompanying explanations. Changes have been made in regard to the lateral spinothalamic tract, arrangement of the fibers in the thalamus, position of the fibers in the medial lemniscus, and fiber connections between the vestibular nuclei and flocculonodular lobe of the cerebellum. Other minor changes have been made in the text to achieve a greater clarity of presentation. The author has made every effort to present the neural systems in a simplified manner, and has felt it necessary in some instances to fill in on the basis of logical assumption where actual knowledge is lacking. This in no way detracts from the usefulness of his charts.

E F C

Hemorrhagic Diseases Photo-Electric Study of Blood Coagulability By KAARE K NYGAARD, M D 320 pages, 24.5 × 16.5 cm C V Mosby Co, St Louis 1941 Price, \$5.50

This monograph is concerned chiefly with the exposition of a new technic, devised by the author, based on the photo-electric principle for the study of blood coagulation. It is divided into three parts. Part I concerns itself with a historical review of methods for determining the coagulability of the blood. These methods have been conveniently divided into four groups, namely, those based on viscosimetry, optical methods, Van Allen's method, and plasma coagulability tests. The author's method falls into the second group. Succeeding chapters in Part I deal with fundamental principles of the photo-electric method. A description of the instrument devised by

the author, the photelgraph, and a discussion of photelgraph tracings known as coagelgrams. In brief, the technic consists in placing recalcified citiated plasma in the photelgraph which is designed to record automatically, in the form of a tracing, the succeeding changes in density of the fluid as it progresses from a liquid state to a gel. Time intervals are ruled on the specially prepared paper and various portions of the graph are marked by letters much in the manner of the electrocardiograph. The significance of various portions of the graph is considered. In Part II are included chapters discussing, with particular reference to the photelgraph technic, various experimental investigations on the coagulability of blood plasma. Part III deals with a study of various hemorrhagic diatheses by this procedure.

Important aspects of the problem of blood coagulation still urgently demand solution. New technics are always of value in advancing the horizons of knowledge. However, comparatively little new data concerning either of these fundamental problems or their abnormalities in the hemorrhagic blood dyscrasias have been added by this procedure. The volume represents a considerable amount of carefully done work. It can be recommended to all students of this question. Extensive bibliographies at the end of each chapter are an excellent feature of the book.

M S S

COLLEGE NEWS NOTES

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College

Dr F Gorham Brigham, Brookline, Mass
Dr William H Bunn, Youngstown, Ohio
Dr Curtis Crump, Asheville, N C
Dr Samuel L Gabby, Elgin, Ill

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of Publications by Members are gratefully acknowledged

Books

Dr Oscar G Costa-Mandry, F A C P, San Juan, P R—"Manual De Laboratorio de Salud Publica"

Reprints

Dr Edward W Anderson, F A C P, Des Moines, Iowa—1 reprint,
Dr Irving Greenfield (Associate), Brooklyn, N Y—2 reprints,
Dr Augustus A Hall, F A C P, Columbus, Ohio—1 reprint,
Dr Rudolph H Kampmeier, F A C P, Nashville, Tenn—42 reprints,
Dr Manfred Kraemer, F A C P, Newark, N J—5 reprints,
Dr William G Leaman, Jr, F A C P, Philadelphia, Pa—1 reprint,
Dr Robert C Page (Associate), Mount Vernon, N Y—2 reprints,
William C Pollock, F A C P, Lieut Col (M C), U S Army—2 reprints,
Dr Hugh P Smith, F A C P, Greenville, S C—1 reprint,
Dr Samuel E C Turvey, F A C P, Vancouver, B C, Canada—1 reprint,
Dr Edwin E Ziegler, F A C P, Boston, Mass—2 reprints

NOMINATIONS FOR A C P ELECTIVE OFFICES

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1942-43, are herewith announced and published

President-Elect	Ernest E Irons, Chicago, Ill
First Vice President	Charles H Cocke, Asheville, N C
Second Vice President	Henry R Carstens, Detroit, Mich
Third Vice President	A Comingo Griffith, Kansas City, Mo

The election of nominees shall be by the members of the College at its Annual Business Meeting, St Paul, Minn, April 23, 1942 These nominations do not preclude nominations made from the floor at the Annual Meeting itself Nominations

for members of the Board of Regents and members of the Board of Governors will be presented at the Annual Business Meeting

Respectfully submitted,
 F Gorham Brigham, Boston, Mass ,
 T Homer Coffen, Portland, Ore ,
 J Morrison Hutcheson, Richmond, Va ,
 Warren Thompson, Omaha, Nebr ,
 Edward L Bortz, *Chairman*, Philadelphia, Pa
Committee on Nominations

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

The following Boards have announced schedules of their examinations as follows

AMERICAN BOARD OF INTERNAL MEDICINE

William S Middleton, M D , Secretary
 1301 University Ave
 Madison, Wis

Written Examinations October 19, 1942, applications for admission must be filed before September 1, 1942

Oral Examinations St Paul, Minn, April, 1942, in advance of the meeting of the American College of Physicians, Philadelphia, Pa, June, 1942, in advance of the meeting of the American Medical Association in Atlantic City

AMERICAN BOARD OF PATHOLOGY

F W Hartman, M D , Secretary
 Henry Ford Hospital
 Detroit, Mich

Written and Oral Examinations. Washington University, St Louis, Mo, March 30-31, 1942

AMERICAN BOARD OF PEDIATRICS

C A Aldrich, M D , Secretary
 707 Fullerton Ave
 Chicago, Ill

Oral Examinations. Chicago, Ill, November 2-3, 1942, in advance of the meeting of the American Academy of Pediatrics, applications for admission must be filed before July 3, 1942

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

Walter Freeman, M D , Secretary
 1028 Connecticut Ave, N.W
 Washington, D C

Written Examinations Boston, Mass, probably May 15-16, 1942, in advance of the meeting of the American Psychiatric Association; New York, N Y, December, 1942

AMERICAN BOARD OF RADIOLOGY

B R Kirklin, M D , Secretary
 Mayo Clinic
 Rochester, Minn

Oral Examinations. Atlantic City, N J, June 4-6, 1942, November, 1942 (date and place not yet selected)

For further details and application forms communicate with the respective secretaries

REGIONAL MEETING OF KENTUCKY MEMBERS

Fellows and Associates of the American College of Physicians of Kentucky held their annual regional meeting at Louisville January 10, 1942. At two o'clock in the afternoon the following clinical program was given at the Louisville City Hospital. Dr J. Richard Gott, Jr., F A C P, was in charge of arrangements.

"Observations of a Case of Subacute Bacterial Endocarditis Treated by Artificially Induced Hypothermia"—Herbert L. Clay, M D

"A Preliminary Appraisal of the Five-Day Treatment of Syphilis"—Adolph B. Loveman, M D (Associate, A C P), Fred Hathaway, M D

"Peritoneoscopy"—Joseph E. Hamilton, M D

"Gelatin as a Substitute for Blood Plasma"—Harold Gordon, M D, F A C P

Clinico-Pathological Conference—A. J. Miller, M D, F A C P, Morris Flexner, M D, F A C P

An evening social hour and dinner were held at the Pendennis Club. Dr Chauncey W. Dowden, F A C P, Governor for Kentucky, was Toastmaster.

Forty-six College members were in attendance, and the meeting was considered a thoroughly successful one, except for the disappointment of the inability of the President and President-Elect of the College to be present.

NEW ENGLAND REGIONAL MEETING, AMERICAN COLLEGE OF PHYSICIANS

In the fall of 1941 the Governors of the six New England states decided to hold a regional meeting in New England every year if war conditions permit. The first of these took place in Providence on January 14, 1942. It was a one day affair beginning with clinics at the Rhode Island Hospital from 10 to 12:30, lunch at the hospital, an afternoon scientific session at the Rhode Island Medical Library from 2 to 5:30, and a shore dinner at the Squantum Club in the evening.

The morning clinics were well attended and proved interesting. They consisted of a number of short talks, demonstrations and reports of cases by members of the staff and a few clinicians from other local hospitals. This session was arranged and conducted by Dr Charles F. Gormly, F A C P, Physician-in-Chief of the Medical Department.

In the afternoon the following program was presented under the chairmanship of Dr Alex M. Burgess, F A C P, Governor for Rhode Island.

"Eight Cases of Essential Pentosuria"—Dr R. O. Bowman and Dr I. A. Beck, Providence

"Application of Bone Marrow Biopsy to Certain Clinical Diagnostic Problems"—Dr R. J. Williams (Associate), Providence

"Pernicious Anemia Complicated by a Malignant Polyp of the Stomach"—Dr J. W. Wentworth and Dr C. T. Bingham, F A C P, Hartford

"Sulfanilamide in the Treatment of Scarlet Fever"—Dr K. K. Gregory (Associate), Providence

"The Modern Management of Addison's Disease"—Dr Michael F. DeMaio, Providence

"Experimental Liver Necrosis Produced by Tannic Acid (and its clinical correlation)"—Dr R. E. Kendall (Associate), Hartford

"Sarcoid from X-ray Standpoint"—Dr R. T. Ogden (Associate), Hartford

"The Circle of Willis and Its Aneurysms"—Dr C. A. McDonald, Providence, and Dr Milton Korb, Boston

A paper on encephalitis which was to be given by Dr John Dingle of Boston was omitted as Dr Dingle was detained in the south on government business, and Dr De Maio's paper was substituted

In the evening, following one of the famous Rhode Island shore dinners at the Squantum Club, Dr Roger I Lee, F A C P, President of the College, and Mr E R Loveland, Executive Secretary, spoke. An address by Dr O H Perry Pepper, F A C P, Philadelphia, had to be omitted as Dr Pepper was detained in Washington. Dr Henry Heyl, lately neuro-surgeon to the American Hospital in Britain, who was stationed at Birmingham during the period of the most severe raids, gave an interesting talk on "Recent Medical Experiences in England." President Henry M Wriston of Brown University and The Very Rev John J Dillon, President of Providence College, were guests. Dr Gormly was Toastmaster.

There were 95 physicians registered for the afternoon session, and 96 tickets for the dinner were issued. The meeting was sponsored by the Governors of the six New England states and arranged by the Governor for Rhode Island with the aid of the following committee: Charles F Gormly, F A C P, General Chairman, Elihu S Wing, F A C P, William S Streker, F A C P, and John F Kenney, F A C P.

It was decided that the meeting next year will, if conditions permit, be held in Hartford, Connecticut.

In early January the Finlay Institute of the Americas was formed in Havana, Cuba. The commission from the United States consisted of Dr James E Paullin, F A C P, Atlanta, Ga., Dr Edgar Mayer, F A C P, New York City, Dr Thomas Mackie, F A C P, New York City, Dr Milton Kahn, New York City, and Dr Morris Fishbein, Chicago. On the Cuban commission were three members of the College, namely, Dr Angel Vieta, F A C P, Dr Felix Hurtado Galtés, F A C P, and Dr Octavio Montoro Saladrigas, F A C P, all of Havana. A plan was formulated for the participation of the Americas in the promotion of the scientific and cultural relationships of the medical groups in the two countries and in the Americas. Dr Paullin was named Chairman of the Scientific Committee of the United States.

Under the direction of the Advisory Committee on Postgraduate Courses, of which Dr Edward L Bortz, F A C P, Philadelphia, Pa., is Chairman, the American College of Physicians arranged a series of "Postgraduate Nights" at the United States Naval Hospital in Philadelphia, February 2-5. The following program was presented with Henry L Dollard, F A C P, Captain (M C), U S Navy, Commanding Officer of the Naval Hospital, presiding:

February 2, 1942

GENERAL MEDICINE

- "Medical Emergencies"—GEORGE MORRIS PIERSOL, M D, F A C P, Vice Dean and Professor of Medicine, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.
- "Prophylaxis and Treatment of Virus Diseases"—HOBART REIMANN, M D (By Invitation), Magee Professor of Practice of Medicine and Clinical Medicine, Jefferson Medical College, Philadelphia, Pa.
- "Fatigue"—CHARLES L BROWN, M D, F A C P, Professor of Medicine and Head of Department of Medicine, Temple University School of Medicine, Philadelphia, Pa.
- "Borderline Metabolic Deficiencies"—G HARLAN WELLS, M D, F A C P, Professor of Medicine, Hahnemann Medical College, Philadelphia, Pa.

February 3, 1942

CARDIOVASCULAR DISORDERS

- "Effort Syndrome"—WILLIAM D. STROUD, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine and School of Medicine, Philadelphia, Pa
- "Criteria of Organic Heart Disease in Recruits"—FRANCIS CLARK WOOD, M.D., F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa
- "Some Forms of Cardiac Derangement During War Service"—THOMAS M. McMILLAN, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa
- "Cardiovascular Problems in Aviation"—J. M. BACHULUS, M.D. (By Invitation), Lieutenant Commander (M.C.), U.S.N., Senior Medical Officer and Flight Surgeon, U.S. Naval Air Station, Lakehurst, N.J.
-

February 4, 1942

NEUROPSYCHIATRY

- "Personality Deviations"—EDWARD A. STRECKER, M.D., F.A.C.P., Professor of Psychiatry and Chairman of Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Pa
- "Early Signs of Psychoses"—EARL D. BOND, M.D. (By Invitation), Vice Dean for Neurology-Psychiatry, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa
- "Traumatic Neuroses"—GEORGE WILSON, M.D. (By Invitation), Professor of Clinical Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pa
- "Malingering"—BALDWIN L. KEYES, M.D., F.A.C.P., Clinical Professor of Psychiatry, Jefferson Medical College, Philadelphia, Pa
-

February 5, 1942

CHEMOTHERAPY

- "Pharmacology and Toxicology"—HARRISON F. FLIPPIN, M.D., F.A.C.P., Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa
- "Surgical Infections"—JOHN S. LOCKWOOD, M.D. (By Invitation), Associate in Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa
- "Medical Infections"—JOHN A. KOLMER, M.D., F.A.C.P., Professor of Medicine, Temple University School of Medicine and School of Dentistry, Philadelphia, Pa
- "Urinary Tract Infections"—CHARLES UHLE, M.D. (By Invitation), Associate in Urology, University of Pennsylvania School of Medicine, Philadelphia, Pa

At the completion of the above program, the following letter was received from the Commanding Officer of the Naval Hospital

February 6, 1942

"DR EDWARD L BORTZ, *Chairman*
Advisory Committee on Postgraduate Courses
American College of Physicians
Philadelphia, Pa

"*Dear Dr Bortz*

"The Series of four 'Postgraduate Nights,' just completed last night at the Naval Hospital, Philadelphia, was an unqualified success, and I hope the idea may be the seed of a country-wide movement in the direction of intensive graduate instruction to medical officers of the armed forces

"In time of peace, the Bureau of Medicine and Surgery of the Navy Department constantly maintains a number of medical officers under instruction in various graduate schools of medicine Under war conditions it is not practicable to spare officers for weeks or months Furthermore, in time of war there is a rapid and great increase in the size of the Medical Corps, active and reserve Therefore, it would appear that the matter of graduate and refresher instruction should be carried to the men in the field, exactly as was done in the 'Postgraduate Nights'

"To you as the organizer and director of the course at the Naval Hospital, I extend my sincere thanks and congratulations

"With kindest regards

Very Sincerely,
(Signed) HENRY L DOLLARD,
Captain, (MC), U S Navy,
Commanding U S Naval Hospital,
Philadelphia, Pa "

Harry G Armstrong, F A C P, Major (MC), U S Army, in charge of research at the School of Aviation Medicine, Randolph Field, Tex, has been named to receive the John Jeffries Award given by the Institute of the Aeronautical Sciences

This Award, given annually "for outstanding contributions to the advancement of aeronautics through medical research," will be conferred on Major Armstrong in recognition of his pioneering studies on the physiological and psychological effects of flying at high altitude and in high speed maneuvers He was one of the first to recognize and accurately to describe some specific medical results of flying, such as aero-neurosis, a kind of mental and physical fatigue experienced by flyers under certain conditions, aero-otitis, an effect of high altitude and acrobatic flying on the human middle ear, and aero-embolism, a reaction similar to the "bends" suffered by deep sea divers which affects pilots who climb to high altitudes too rapidly and without proper safeguards

Major Armstrong is a member of the Aero Medical Association, the Association of Military Surgeons and the American Medical Association He is a Fellow of the American College of Physicians and of the Institute of the Aeronautical Sciences He was chosen to receive the John Jeffries Award for 1941 by a committee consisting of Dr G. W Lewis, Director of Research of the National Advisory Committee for Aeronautics, Gill Robb Wilson, President of the National Aeronautic Association, Edgar S Gorrell, President of the Air Transport Association of America, John R Poppen, F A C P, Captain (MC), U S Navy, President of the Aero Medical Association, Frank W Caldwell, President of the Institute of the Aeronautical Sciences, and Lester D Gardner, President of the Aeronautical Archives of the Institute

The American Association of Industrial Physicians and Surgeons, and the American Industrial Hygiene Association will hold their joint Annual Convention in Cin-

cinnati, April 13-17, 1942 The central purpose of the meeting will be to provide a five-day institute for the interchange and dissemination of information on new problems as well as for the consideration of up-to-date methods of dealing with those that are well known Important medical and hygienic problems associated with the present huge task of American industry will be presented and discussed in clinics, lectures, symposia, and scientific exhibits

"Laboratory Policies and Requirements in the Examination of Water" is the title of a paper in the Puerto Rico Health Bulletin for December, 1941, by Dr O Costa Mandry, F A C P Dr Costa Mandry is Director of the Public Health Laboratories of the Puerto Rico Department of Health

Among the speakers at the 4th Annual Congress on Industrial Health, sponsored by the Council on Industrial Health of the American Medical Association, January 12-14, 1942, were

Dr Andrew C Ivy, F A C P, Chicago, Ill—"The Physiology of Work",
 Dr T Lyle Hazlett, F A C P, East Pittsburgh, Pa—"Industrial Health—A Separate Discipline",
 Dr Walter L Bierring, F A C P, Des Moines, Iowa—"Postgraduate Education in Industrial Health",
 Dr George E Wakerlin, F A C P, Chicago, Ill—"Pulmonary Capacity Tests in Health and Disease"

A report on "Vitamin Administration in Industry" was presented by representatives of the Council on Foods and Nutrition and the Council on Industrial Health of the American Medical Association Dr James S McLester, F A C P, Birmingham, Ala, and Dr Russell M Wilder, F A C P, Rochester, Minn, were among the members of these Councils who prepared this report

Dr Walter Lindsay Niles, of New York, N Y, was elected a Fellow of the American College of Physicians on December 14, 1941, but notification of his death suddenly on December 22, 1942, removes his name from the Roster before official announcement of elections could be published

Dr William Nimeh, F A C P, Mexico City, Mexico, on a recent visit to the United States read a paper entitled, "Contribution of the Arabs to Medicine," at a meeting of the Staff of the Mayo Clinic

Dr Charles F Goimly, F A C P, Providence, was recently appointed a member of the Advisory Council to the State Department of Health, by the Governor of Rhode Island

The Alumni Association of the College of Medical Evangelists held its 8th Annual Postgraduate Assembly at the White Memorial Hospital, Los Angeles, Calif, December 7, 1941 Among those who participated in the program were

Dr Thomas Addis, F A C P, San Francisco, Calif—"Diagnosis and Treatment of Nephritis in Group Practice",
 Dr Roy E Thomas, F A C P, Los Angeles, Calif—"Atypical Pneumonia",

Dr Hans Lissner, F A C P, San Francisco, Calif—"Indications for and Modes of Administering Testosterone Compounds in the Male",

Dr Percival A Gray, Jr, F A C P, Santa Barbara, Calif—"Office Management of the Diabetic Patient"

Dr Philip F Barbou, F A C P, Louisville, Ky, spoke on "Active and Passive Immunization of Tetanus" and "Rehabilitation of Poliomyelitis Patients" at a recent meeting of the Georgia Pediatric Society

Dr James Alex Miller, F A C P, Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, delivered the Linsly R Williams Memorial Lecture of the New York Academy of Medicine, November 13, 1941. The subject of Dr Miller's address was "Tuberculosis The Known and the Unknown"

Dr Tom D Spies, F A C P, Associate Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio, was presented the Award of Distinction of the American Pharmaceutical Manufacturers' Association at its meeting in Washington, D C, December 8, 1941. This award is made annually to an investigator who, in the opinion of the committee, has made a fundamental contribution to public health in the field of drug therapy. The award was given to Dr Spies in recognition of his work on nicotinic acid

Dr Carleton B Peirce, F A C P, Montreal, Que, has been appointed Associate Professor of Radiology at McGill University Faculty of Medicine

Dr Elmer L Sevringhaus, F A C P, College Governor for Wisconsin, has been elected an honorary foreign member of the National Academy of Medicine of Buenos Aires

The Thomas Drake Martinez Cardeza chair of clinical medicine and hematology has been established at Jefferson Medical College of Philadelphia. Dr Harold W Jones, F A C P, has been named the first incumbent. Funds have been provided by Thomas Drake Martinez Cardeza to carry on the work of the Charlotte Drake Cardeza Foundation for the study and investigation of diseases of the blood and allied conditions

NAVY NEEDS ADDITIONAL MEDICAL OFFICERS

The Surgeon General of the Navy announces the need for additional medical officers of the U S Naval Reserve who are qualified in Medical Department specialties, including that of Internal Medicine. Applicants for appointment in the Medical Corps of the U S Naval Reserve may obtain full and detailed information concerning such appointments by applying to the Commandant of the Naval District in which they reside. The maximum age limitation for appointments in the Medical Corps of the U S Naval Reserve is fifty years of age.

Fellows of the American College of Physicians, who are physically and in other respects qualified for appointments, may apply for appointments in the Volunteer, Special Service Class of the U S Naval Reserve in their specialty (Internal Medicine, or other specialties in Internal Medicine).

If the address of the Commandant of the Naval District is not known it is suggested prospective applicants address a communication to the Bureau of Medicine

and Surgery, Navy Department, Washington, D C, for information concerning appointments in the Medical Corps of the U S Naval Reserve

POSTGRADUATE COURSE IN TUBERCULOSIS WITHDRAWN

Postgraduate course No 11, Tuberculosis, scheduled for the period April 13 to 18, 1942, at the University of Colorado School of Medicine and Hospitals, Denver, Dr James J Waring, F A C P as Director, was withdrawn February 6 due to conditions arising primarily out of the war Some of the instructors were momentarily expecting to be called to active service, and, furthermore, the registration to that date had been inadequate The director of the course and his associates deeply regret this necessary action The College also expresses keen disappointment because this course would have been an exceedingly good one and had been especially organized for a group of tuberculosis physicians in the College membership

OBITUARIES

DR FREDERICK TAYLOR LORD

Dr Frederick Taylor Lord, F A C P, was born in Bangor, Maine, January 16, 1875 He died in Boston, November 4, 1941 His life was one of quiet and sustained devotion to his professional work, to his family, and to his friends His point of view toward medicine was that of the teacher and of the scholar Always he sought to learn something new Always he sought to make what he had learned available to others He leaves behind many pupils grateful for the wise instruction which he gave, for the example of meticulous thoroughness which he set, and for the kindly friendship with which he blessed all those who shared his work He possessed those qualities which Lord Tweedsmuir once said were necessary to the successful working of democracy—humility, humanity and humour The last of these was often manifested by a twinkle in his eye of almost elfish jollity

From Harvard he received his A B in 1897, and his M D in 1900 He served as Medical House Officer at the Massachusetts General Hospital in 1900 and 1901, and he remained on the staff of that institution, in one capacity or another, until his death From 1912 to 1935 he was Visiting Physician, and after 1935 a member of the Board of Consultation

He joined the teaching force of the Harvard Medical School in 1905 as Instructor in Clinical Medicine, and throughout his life he participated actively in the work of the School, as well as in that of the hospital In 1930 he was made Clinical Professor of Medicine, and in 1935, Clinical Professor of Medicine, Emeritus

Although he served hospital and school largely without pay, and made his living in the private practice of medicine, as had the great clinical teachers of the past, the chief focus of his work was in these institutions In addition to his constant interest in dispensary and bedside teaching, throughout his life he always had some piece of research in progress Early in his

career he persuaded Dr J Homer Wright to give him a laboratory in the Allen Street House of the hospital. In this cubby-hole—it was little more—he was to be found whenever he had spare time, working like a beaver on some problem such as the role of actinomyces in dental caries. (Contribution to the etiology of actinomycosis. The Experimental production of actinomycosis in guinea pigs inoculated with the contents of carious teeth, Boston Med and Surg Jr, 1910, clxiii, 82.)

When in 1917 Dr Edsall was able to secure decent space for clinical research, Dr Lord was given a somewhat ampler laboratory in which, over a period of years, he conducted with the able collaboration of Dr Robert N Nye, a series of valuable studies on the biology of the pneumococcus.

Within the field of internal medicine, diseases of the chest were always Dr Lord's special interest. In 1907 he was entrusted by Osler to write the chapter on Diseases of the Pleura in the seventh volume of the system on "Modern Medicine," and in two succeeding editions in 1913 and 1925 he contributed the chapter on Influenza. In 1915 was published his "Diseases of Bronchi, Lungs and Pleura," which ever since has remained an important text on these subjects.

He was early engaged in the fight against tuberculosis, serving for many years as President of the Channing Home, one of the first special hospitals for the care of patients with advanced tuberculosis, and in the public aspects he shared by serving on Advisory Committees of the State Department of Public Health and the Boston City Health Department, and through his leadership in various societies.

When anti-pneumococcic serum appeared on the scene in 1913, Dr Lord took an active part in studying its action on patients and, with the aid of The Commonwealth Fund, in making it available for use by physicians throughout the state. When chemotherapy arrived he studied that with equal intensity. He collaborated closely with Dr Roderick Heffron in these problems, and with him wrote several books on the subject.

In World War I Dr Lord went to the Balkans as a member of the American Red Cross Commission to Serbia, for the relief and rehabilitation of the small remaining Serbian population.

In World War II he was doing his bit by compiling data on the qualifications of physicians in Massachusetts, and by making studies on the evaluation of rabbit and horse serum in the higher types of pneumococcus pneumonia.

In addition to the usual medical societies, Dr Lord belonged to the Association of American Physicians, the Interurban Clinical Club, of which he was a charter member, and in 1928 President, the American Society for Clinical Investigation; the American Clinical and Climatological Association, the American Association for Thoracic Surgery, of which he was President in 1932, the National Tuberculosis Association, of which he was Vice-President in 1938-39, and the Massachusetts Tuberculosis League, of

which he was President in 1928. He had been a Fellow of the American College of Physicians since 1929.

Thus was his life full of good works, and long will the memory of this gentle, kindly, generous physician warm the hearts of those who knew him.

J H M

F M R

DR CHARLES BRADFORD SYLVESTER

Dr Charles Bradford Sylvester, F A C P, of Portland, Maine, died December 18, 1941, as the result of heart and kidney disease.

Dr Sylvester was born in Casco, Maine, February 12, 1865. He was graduated from Bridgton Academy in 1884 and five years later was granted a degree in medicine from the Bowdoin Medical School. He served as house physician at the New York Infants Hospital and Randalls Island Hospital in 1889 and 1890 and in the latter year he opened an office in the town of Harrison, Maine, where he practiced, with a single interruption, for 28 years. The interlude was provided by a graduate course in pathology at the Harvard Medical School in the years 1909 and 1910. Although his practice was perforce a general one, including obstetrics and minor surgery, the doctor's main interest was in medicine and he came to enjoy a considerable reputation as a medical consultant among the physicians in the region where he lived. He was President of the Oxford County Medical Society in 1908.

Early in 1918 Dr Sylvester was given a commission in the Medical Reserve Corps of the U S Army. During the next two years he was on duty in the Tuberculosis Service at Camps Oglethorpe and Sevier and at General Hospitals No 16 and No 17. His interest in military medicine continued for the remainder of his life, he maintained his commission in the Medical Reserve Corps until he was retired because of age in 1929 with the rank of Lieutenant Colonel.

The duty assignment given Dr Sylvester was entirely to his liking, it served to stimulate the interest which he already had in tuberculosis and this changed the course of his life. When he was discharged from service, in spite of the fact that he was nearly fifty-five years of age, he decided to settle in the City of Portland, Maine, and to confine his practice to internal medicine. The decision was a happy one. His fine personality, his ability and experience made him a popular consultant in diseases of the lungs. Within a short time he discovered a new interest in allergic respiratory diseases. As a member of a chest team, he visited and helped hold clinics in many of the cities and towns of the state. His energy and youthful enthusiasm seemed without limit. Our present system of tuberculosis survey of school children in Maine we owe in large part to the efforts of Dr Sylvester. In recent years he conducted ragweed pollen surveys in Maine, the results of which were published in the New England Journal of Medicine.

Dr Sylvester was Consulting Physician and Clinician in the Outpatient Department of the Maine General Hospital. He was a former President of the Cumberland County Medical Society, the Maine Medical Association, and the Maine Public Health Association. In 1939 he received the Maine Medical Association medal for fifty years of active medical practice. He was elected to Fellowship in the American College of Physicians in 1930. He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, a Fellow of the American Academy of Tuberculosis Physicians, Director for Maine of the National Tuberculosis Association, a member of the Portland Medical Club, and President of the Board of Trustees of Bridgton Academy.

In spite of an active practice and his part in public health work, Dr Sylvester found time to keep in touch with civic affairs, although he did not hold public office. He offered to his patients the sympathetic interest and understanding of the family physician, patients were never cases to him. His dealings with other practitioners were always above criticism. He loved youth, as he himself remained a youthful man, and younger doctors who knew him remember with gratitude his advice and help. In many respects Dr Sylvester exemplified the finest attributes of the physician.

E H DRAKE, M D, F A C P,
Governor for Maine

DR PETER A REQUE

Dr Peter Augustin Reque was born in 1869 at New Lisbon, Wisconsin, and died on December 4, 1941, in the Long Island College Hospital, Brooklyn, N Y. He received his B A degree from Lutheran College, Decorah, Iowa, M D in 1896 from the University of Vermont College of Medicine, at one time he was on the faculty of the Long Island College Hospital and his practice was limited primarily to dermatology and urology.

Dr Reque was a member of the Kings County Medical Society, Brooklyn Urological Society, South Brooklyn Medical Society, New York State Medical Society, the American Medical Association and he became a Fellow of the American College of Physicians in 1920. He served in France in the first World War with the rank of Major. He was a member of Cadaceus Post 818, a member of the American Legion, and was buried in Arlington National Cemetery.

CHARLES F TENNEY, M D, F A C P,
Governor for Eastern New York

PROGRAM
TWENTY-SIXTH ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
ST. PAUL, MINN

April 20-24, 1942

GENERAL SESSIONS AND LECTURES

Roger I Lee, President

ST PAUL COMMITTEE ON ARRANGEMENTS

John A Lepak, General Chairman

James N Dunn	Gordon R Kamman
Everett K Geer	Harold E Richardson
Charles N Hensel	Edward Schons

COMMITTEE ON CLINICS

Harold E Richardson, Chairman

Alfred Hoff, Co-Chairman

Joseph F Borg	Bethesda Hospital
Raymond H Beech	Mounds Park Hospital
Lyman R Critchfield	Ancker Hospital
Joseph N Gehlen	Ancker Hospital
John Holt	Ancker Hospital
Lillian L Nye	Ancker Hospital
Harry Ghent	St John's Hospital
Frank G Hedenstrom	Children's Hospital
Max Hoffman	Charles T Miller Hospital
Joseph W Jesion	Northern Pacific Hospital
Harry Oerting	St Luke's Hospital
Joseph M Ryan	St Joseph's Hospital
Benjamin B Souster	Midway Hospital
Cecil J Watson	University Hospitals

COMMITTEE ON HOTELS AND TRANSPORTATION

Gordon R Kamman, Chairman

Harvey O Beek	John P Medelman
Francis W Lynch	Alfred J Ouellette

COMMITTEE ON ENTERTAINMENT

James N Dunn, Chairman

Edward V Goltz, Vice Chairman

Edward C Gibbs	John Meade
Arnold E Naegeli	

COMMITTEE ON AUDITORIUM

Edward Schons, Chairman	
Frederick C Schuldts, Vice Chairman	
J Richards Aurelius	Burtis J Mears
Woodward Colby	Fritz R Pearson
William R McCarthy	Mark E Ryan

COMMITTEE ON PUBLICITY

Charles N Hensel, Chairman	
Robert M Burns, Vice Chairman	
Harold H Fesler	Alex E Venables
Emmet V Kenefick	Benjamin A Weis

COMMITTEE ON PANEL DISCUSSIONS

Everett K Geer, Chairman	
Edward C Gager, Vice Chairman	
John F Briggs	Kano Ikeda
Edgar T Herrmann	George N Ruhberg
Alexander R Hall	J Allen Wilson

COMMITTEE ON LADIES' ENTERTAINMENT

Mrs Edward V Goltz, Chairman	
Mrs J Richards Aurelius	Mrs Alfred Hoff
Mrs John F Briggs	Mrs Kano Ikeda
Mrs James N Dunn	Mrs Gordon R Kamman
Mrs Edward C Gager	Mrs John A Lepak
Mrs Everett K Geer	Mrs Harold E Richardson
Mrs Alexander R Hall	Mrs Edward Schons
Mrs Edgar T Herrmann	Mrs Benjamin B Souster,

HONORARY COMMITTEE

Living Past Presidents

James D Bruce
 O H Perry Pepper
 William J Kerr
 James H Means
 Ernest B Bradley
 James Alex Miller
 Jonathan C Meakins
 George Morris Piersol
 Francis M Pottenger
 S Marx White
 Sydney R Miller
 John H Musser
 Charles F Martin

A WELCOME TO THE AMERICAN COLLEGE OF PHYSICIANS

With hand outstretched in ever welcome greeting to you all,
 We take you to our own and wish you well, hoping the while
 That you may find the hospitality of old Saint Paul
 Something to remember of our frank mid-western style

To this illustrious group, may we say that we are glad indeed
 To have you with us now, adding a luster e'en anew
 To an ever glowing past, which, springing from a tiny seed,
 Now stands a flowering city, where once a forest grew

Proud are we of our heritage, fruits of efforts made by men,
 Hardy pioneers, empire builders, saints and scholars all,
 Who blazed our trails and laid foundations well, that we who follow them
 May bravely bear the torch and write new ere life's shadows fall

See our city from the heights of Cherokee at night,
 Where years ago embattled Indians fought, and looking North,
 See myriads of vari-colored twinkling lights
 Reflected on the river now peacefully flowing forth

Still farther North, in silhouette against emblazoned sky,
 Our State House stands, a symbol of the freedom in our land,
 And to the left, atop a hill, green domed with arms stretched high,
 Saint Paul's Cathedral testifies the love of God for man

Far to the right above the river's bend, the Indian Mounds
 Where dead Sioux Chieftains lie, facing the east against the rising sun,
 Waiting the dawn of life anew in the happy hunting grounds
 Waiting with the Mounds and the river 'til the sands of time are run

This is our city of bluffs and bridges under whose broad spans
 The mighty Mississippi flows silently to the sea
 Upon whose calm expanse is mirrored on history's page
 Journeys of ancient voyageurs for all posterity

These are the things we love, this is our home and for the time
 'Tis yours who gather with us here in common brotherhood,
 Who foster now the theme of "man's humanity to man"
 That in these trying times it seems is little understood

To this grand assemblage gathered, let us rise and give a toast,
 From dawn of day to setting sun, from North, South, East and West,
 Reverberating from our seven hills, Saint Paul the gracious host,
 May ring in pleasant memory forever as the best

J J R

GENERAL INFORMATION

St Paul Headquarters

General Headquarters—Municipal Auditorium

Hotel Headquarters—Hotel Lowry and Hotel St Paul, jointly

The St Paul Municipal Auditorium will be General Headquarters for registration, exhibits, general sessions, panel discussions and special lectures

The Hotel Lowry will be headquarters for Officers, Regents, Governors and Committeemen. However, Hotel St Paul, located near-by, will serve as joint headquarters for members of the College

List of St. Paul Hotels	Blocks from Municipal Auditorium	Rates per day, with private bath	
		Single Room	Doubt Room
HOTEL LOWRY	3½	\$2 50-5 00	\$4 00-5 00
HOTEL ST PAUL	2	2 50-5 00	3 50-5 00
Angus	10	2 00-2 50	2 50-3 50
Capitol Apts	4	2 50	4 00-7 00
Commodore	10	2 50-5 00	5 00-7 00
Frederic	5	1 75-2 50	2 00-3 50
Grand	2	1 75-2 00	2 00
Jewell	4½	2 00	3 50-6 00
Ryan	8	2 00-3 00	2 50-4 00
St Francis	3	2 50-3 50	2 50-3 50

Members should make reservations directly with hotels of their choice. Members of the American College of Physicians, for rates quoted are, in some instances, only for this occasion.

WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing in 1942 (dues, if not paid previously, may be paid at the Registration Bureau)
- (b) All newly elected members
- (c) Medical students pursuing courses at the University of Minnesota School or The Mayo Foundation, upon presentation of cards, or other evidence of registration at these institutions for morning lectures, general sessions
- (d) Members of the staff, including interns, of the hospitals participating in the program, without registration fee, upon presentation of proper identification, exhibits, morning lectures, panel discussions and general sessions
- (e) Members of the Ramsey and Hennepin County Medical Societies, without registration fee, upon presentation of membership cards in their respective societies
- (f) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials
- (g) Qualified physicians who may wish to attend this Session as visitors. Physicians shall pay a registration fee of \$12 00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (the proceedings will be published), included within such fee.

REGISTRATION BUREAU—Temporary Registration Bureau will be located at the Municipal Auditorium on Sunday, April 19, from 2 30 to 5 00 in the afternoon and from 7 00 to 9 00 in the evening. The permanent Registration Bureau will be open daily 8 30 a m to 6 00 p m, Monday to Friday, April 20 to 24.

REGISTRATION BLANKS FOR ALL CLINICS AND PANEL DISCUSSIONS will be sent to members of the College with the formal program. Members will secure registration blanks at the Registration Bureau during the Session.

BULLETIN BOARDS FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau at the Municipal Auditorium and in the lobby of the headquarters hotels.

TRANSPORTATION—There will be no special convention rates in connection with national transportation. However, in many instances, reduced round trip tickets are in effect from certain localities. Consult your local ticket agent.

Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the meeting

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 4 40 p m , Thursday, April 3, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present

There will be the election of Officers, Regents and Governors and the annual reports of the Secretary-General, Executive Secretary and Treasurer will be presented The President-Elect, Dr James E Paullin, Atlanta, Ga , will be inducted into office

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled as indicated Special meetings will be announced and posted

A *dinner meeting* of the Board of Regents and of the Board of Governors will be held at the Hotel Lowry, Spanish Room, mezzanine floor, Sunday evening, April 19, at seven o'clock

COMMITTEE ON CREDENTIALS

Sunday, April 19, 9 00 a m Municipal Auditorium, mezzanine floor, Executive Secretary's Office

BOARD OF REGENTS

Municipal Auditorium, mezzanine floor

Sunday, April 19, 2 30 p m
Tuesday, April 21, 12 00 m *
Friday, April 24, 12 00 m *

BOARD OF GOVERNORS

Municipal Auditorium, mezzanine floor

Monday, April 20, 5 00 p m
Wednesday, April 22, 12 00 m *

SPECIAL FEATURES

MONDAY, APRIL 20, 1942

THE ANNUAL SMOKER—Directly following the last presentation of the Second General Session on Monday evening, the so-called Annual Smoker of the College will be held in Stem Hall, which adjoins the theater in the Municipal Auditorium

There will be plenty of beer, tobacco, cold foods and refreshments, but, it these will play only a secondary rôle to the renewed friendships, orchestral quartet singing, movies in technicolor of Big Game Hunting in Alaska and the Winter Carnival, and general fun and merry-making

Entertainment Committee firmly believes that the above special Monday features will not only further the social aspects of the College but also enhance the purpose of the Annual Smokers

Fellows and Associates, local and visiting physicians and the technical exhibitors invited to attend the Smoker as guests of the College The registration badge is required for identification

TUESDAY, APRIL 21, 1942

ENTERTAINMENT BY THE RAMSEY COUNTY MEDICAL SOCIETY
—8 00 p m , Theater, Municipal Auditorium In view of there being no scientific

* Buffet luncheon served

program scheduled for Tuesday evening, the Ramsey County Medical Society will act as host to the College and present a program of entertainment, details of which will be revealed at the Session

WEDNESDAY, APRIL 22, 1942

CONVOCATION OF THE COLLEGE—8 30 p m , Theater, Municipal Auditorium All members of the College and those to be received into Fellowship should be present Officers, Regents, Governors and newly elected Fellows who have not yet been received in Fellowship are requested to assemble in the hall immediately above the theater lobby of the Municipal Auditorium at 7 45 o'clock, preparatory to the formation of the procession They will be conducted to their seats by the Marshal of the Convocation promptly at 8 30 It is suggested that all appear in evening clothes

The Convocation is open to all physicians and their families generally A cordial invitation is also issued to such of the general public as may be interested

The Convocation Ceremony will include the President's Address and the Convocational Address, which this year will be delivered by William deB MacNider, Kenan Research Professor of Pharmacology at the University of North Carolina School of Medicine, Chapel Hill, whose title will be "A Consideration of the Factor of Change in the Animal Organism " The award of the John Phillips Memorial Medal for 1942 will be made to Dr John R Paul and Dr James D Trask, jointly, of New Haven, Conn The recipients of the Research Fellowships of the College for 1942 will be announced The newly elected Fellows will be presented by the Secretary-General, Dr George Morris Piersol, and after subscribing to the Fellowship Pledge will be inducted by the President The President's Reception and Dance will follow immediately after the Convocation in the Ballroom (mezzanine floor) of the Lowry Hotel All members and their guests are requested to pass along the receiving line Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception

THURSDAY, APRIL 23, 1942

THE ANNUAL BANQUET of the College will be held in the Ballroom of the Hotel Lowry at eight o'clock Dr John A Lepak, General Chairman of the Session, will be Toastmaster The address of the evening, entitled "Medicine and the Public," will be delivered by Dr William A O'Brien, Director of Postgraduate Medical Education, University of Minnesota.

All members of the College, physicians of St Paul and Minneapolis, visitors attending the Session, guests and friends, with their families, are cordially invited Table reservations for groups may be arranged Orchestral music will enrich this occasion For the benefit of those who are reluctant to attend banquets, because of too much speech-making, let it be known that the Banquet of the American College of Physicians is always a delightful exception Tickets should be purchased at the Registration Bureau by Wednesday afternoon—price, \$4 00

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The wives of the St Paul members of the College cordially invite all the visiting women at the College meeting in St Paul to participate in the special program of entertainment arranged for them

The visiting women are asked to register immediately upon arrival in St Paul at their headquarters on the mezzanine floor, Hotel Lowry There they will receive a program of entertainment and information about theaters, stores, restaurants and places of interest in and around St Paul

It is necessary to make reservations for some of the events on the Ladies' Program

, MONDAY, APRIL 20, 1942

Morning Registration, mezzanine floor, Hotel Lowry

Afternoon 4 00 to 6 00 p m Tea of Welcome at the University Club as guests of the members of the Entertainment Committee and the Ramsey County Medical Auxiliary

3 30 p m Buses leave Hotel Lowry for the University Club. Return at 5 30 p m to Hotel Lowry Bus fare, \$ 50

Evening 9 30 p m Annual Smoker, Stem Hall, Municipal Auditorium (Music, singing, technicolor movies, refreshments)

TUESDAY, APRIL 21, 1942

Morning Free

Afternoon 12 30 p m Luncheon and Style Revue by Schunemans, Albrecht Furs, and Helens, Inc Luncheon in Terrace Cafe, Hotel Lowry Tickets, \$1 00

Evening 8 00 p m Entertainment by the Ramsey County Medical Society in the Theater, Municipal Auditorium

WEDNESDAY, APRIL 22, 1942

Morning 11 00 a m Tour of Radiation Therapy Department at the University of Minnesota and Coffman Memorial Union

Afternoon 1 00 p m Luncheon at Coffman Memorial Union Tickets for luncheon, \$1 00 Bus fare, round trip, \$ 50 Buses leave Hotel Lowry at 10 30 a m and return to hotel at 2 00 p m

Evening 8 30 p m Convocation in the Auditorium Theater, followed by the President's Reception and Dance in the Ballroom, Hotel Lowry

THURSDAY, APRIL 23, 1942

Morning 11 00 a m Breakfast for members and guests, Terrace Cafe, Hotel Lowry

Afternoon 1 30 p m Buses leave Hotel Lowry for a tour of the city to visit some of the many interesting places, such as the Indian Mounds Park, Phalen Park, Como Park Conservatory, State Capitol, Minnesota Historical Building, St Paul Art Gallery and School of Arts, Fort Snelling, Sibley House and the St Paul City Hall and Court House Bus fare, \$ 50

Evening 8 00 p m Annual Banquet of the College in the Ballroom, Hotel Lowry

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the Arena Floor of the Municipal Auditorium From the accompanying diagram, it will be noted that the Exhibit has a highly favorable location and arrangement Members are urged to familiarize themselves with the Exhibit layout and to make it a point to visit all the exhibitors

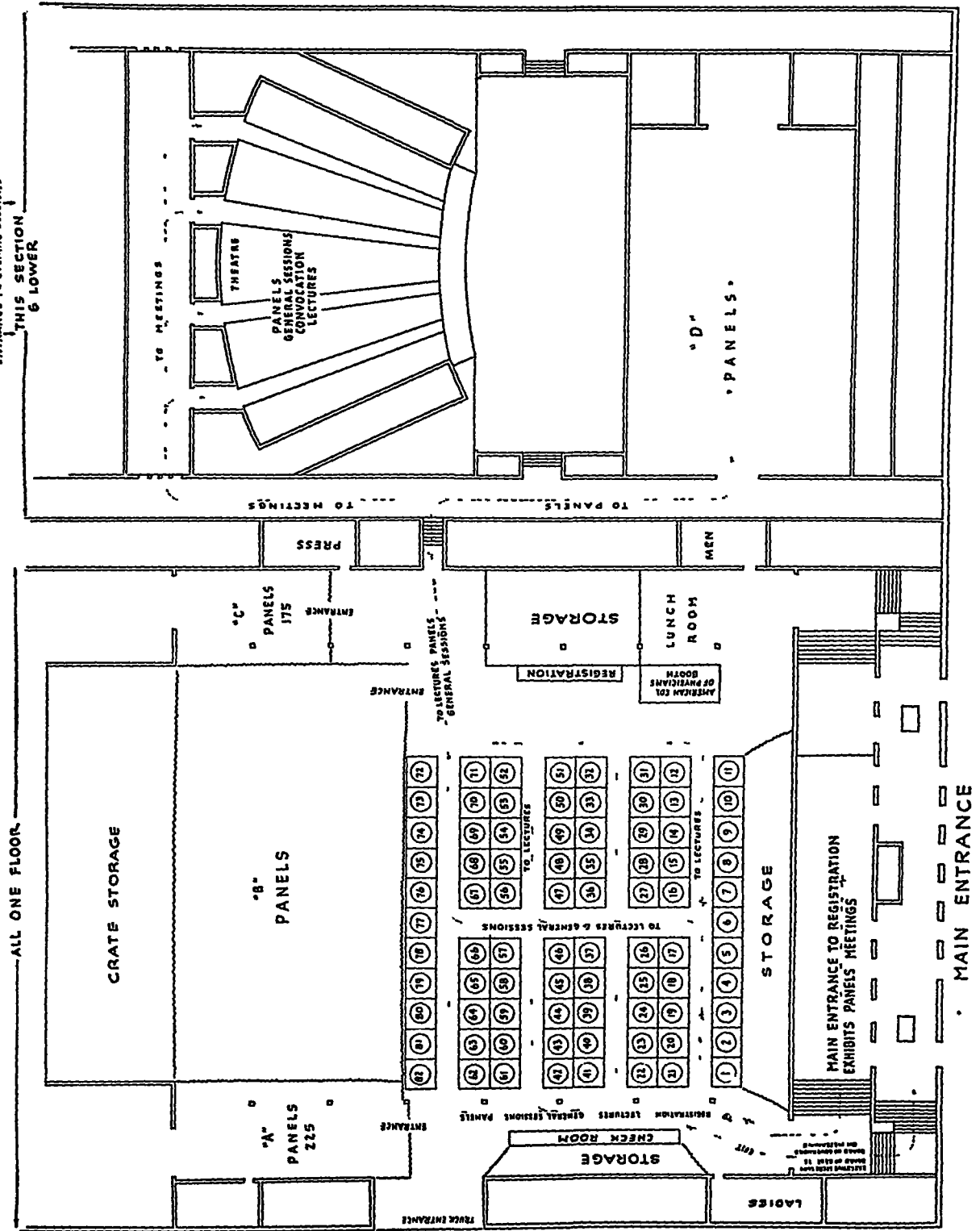
The American College of Physicians has put forward an organized effort to raise the standards of Technical Exhibits All irrelevant products have been eliminated and only firms are invited who present a group of approved products of scientific interest to Internal Medicine and its allied specialties Members of the College will readily distinguish the difference between this Exhibit and the general medical exhibit elsewhere, where frequently all sorts of products irrelevant to the actual practice of medicine are displayed and where methods of high pressure selling are common The Exhibits sponsored by our College warrant the respect and interest of every physician Here conveniently available will be the leading medical books, pharmaceuticals, apparatus and appliances, and many other products or services, making up much of the armamentarium of medical practice These exhibitors and their displays merit your special attention, not only because of their educational value, but because of their contributions to the support of the Annual Sessions of the College

Special intermissions in the general program have been arranged, providing additional time for the inspection of exhibits

LIST OF EXHIBITORS

	<i>Booth No</i>
Ayerst, McKenna & Harrison (U S) Ltd , Montreal, Que	1
E R Squibb & Sons, New York, N Y	2-3
Smith, Kline & French Laboratories, Philadelphia, Pa	4-5
D Appleton-Century Co , Inc , New York, N Y	6
The Wm S Merrell Company, Cincinnati, Ohio	7-8
Winthrop Chemical Company, Inc , New York, N Y	9-10
Warren E Collins, Inc , Boston, Mass	11
J B Lippincott Company, Philadelphia, Pa	12
Frederick Stearns & Company, Detroit, Mich	13
Devereux Schools, Devon, Pa	14
Lederle Laboratories, Inc , New York, N Y	15
The Williams & Wilkins Company, Baltimore, Md	16
The Maltine Company, New York, N Y	17
The Cream of Wheat Corporation, Minneapolis, Minn	18
Davies, Rose & Company, Limited, Boston, Mass	19
The Medical Bureau, Chicago, Ill	20
Paul B Hoeber, Inc , New York, N Y	21
Oxford University Press, New York, N Y	22
White Laboratories, Inc , Newark, N J	26
The Armour Laboratories, Chicago, Ill	27
Abbott Laboratories, North Chicago, Ill	28
F A Davis Company, Philadelphia, Pa	29
Schering Corporation, Bloomfield, N J	30
John Wyeth & Brother, Inc , Philadelphia, Pa	31
Lea & Febiger, Philadelphia, Pa	32
General Electric X-Ray Corporation, Chicago, Ill	33-34
American Hospital Supply Corporation, Chicago, Ill	35
William R Warner & Company, Inc , New York, N Y	36
Sharp & Dohme, Philadelphia, Pa	37-38-39-40
The Arlington Chemical Company, Yonkers, N Y	41
Jones Metabolism Equipment Co , Chicago, Ill	42
Sandoz Chemical Works, Inc , New York, N Y	44
Hoffmann-La Roche, Inc , Nutley, N J	45
Bilhuber-Knoll Corp , Orange, N J	46
Eli Lilly & Company, Indianapolis, Ind	47-48-49
Cameron Heartometer Co , Chicago, Ill	50
Year Book Publishers, Inc , Chicago, Ill	51
W B. Saunders Company, Philadelphia, Pa	52
Ciba Pharmaceutical Products, Inc , Summit, N J	53
Thos Leeming & Co , New York, N Y	54
Merck & Co Inc , Rahway, N J	55-56
The C V Mosby Company, St Louis, Mo	57
Hamilton Manufacturing Company, Two Rivers, Wis	58-59
Cambridge Instrument Co , Inc , New York, N Y	61
Gerber Products Company, Fremont Mich	62
Cameron Surgical Specialty Company, Chicago, Ill	67
Becton, Dickinson & Company, Rutherford, N J	69-70
Sanborn Company, Cambridge, Mass	71

THIS SECTION
6 LOWER



PROGRAM OF THE ST PAUL MEETING

OUTLINE OF THE ST. PAUL SESSION

Auditorium events are indicated in bold type

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 20	April 21	April 22	April 23	April 24
9 00 a m to 11 30 a m	Morning free Registration, Exhibits, etc	Hospital Clinics	Hospital Clinics	Hospital Clinics	Hospital Clinics
		Morning Lectures (9 30- 11 30)	Morning Lectures (9 30- 11 30)	Morning Lectures (9 30- 11 30)	Morning Lectures (9 30- 11 30)
12 00 m to 1 15 p m		Panel Discussions	Panel Discussions	Panel Discussions	Panel Discussions
1 15 p m to 2 15 p m	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2 15 p m to 5 00 p m	1st General Session	3d General Session	4th General Session	5th General Session	6th General Session
5 00 p m to 8 00 p m	Dinner	Dinner	Dinner	Annual Business Meeting	
8 00 p m to 11 00 p m	2d General Session followed by SMOKER		CONVOCATION, followed by President's Reception	ANNUAL BANQUET	

	<i>Booth No</i>
Riedel—de Haen, Inc , New York, N Y	72
The Borden Company, New York, N Y	73
Mead Johnson & Company, Evansville, Ind	74
Burroughs Wellcome & Co (U S A) Inc , New York, N Y	75
The Mennen Company, Newark, N J	76
H J Heinz Company, Pittsburgh, Pa	77
Parke, Davis & Company, Detroit, Mich	82

(As this program goes to press, the following spaces are unassigned 23, 24, 25, 43, 60, 63, 64, 65, 66, 68, 78, 79, 80 and 81)

GENERAL SESSIONS

"Medical Horizons" is the general theme of this program The program of the General Sessions complements that of the clinics, panels and lectures Certain timely topics are taken from the great wealth of medical advances This program includes, among others, a discussion of aviation medicine and a discussion of the problems of old age In some instances, the program represents continued reports on communications made at previous meetings of the College At the New Orleans meeting of the College, Professor E O Lawrence, in the Convocation Address, discussed the cyclotron, in this program, we have a report of some of the clinical applications of that address

GENERAL SESSIONS PROGRAM

Theater, Municipal Auditorium

FIRST GENERAL SESSION

Monday Afternoon, April 20, 1942

General Chairman, John A Lepak, presiding

p m

2 15 Addresses of Welcome

JOHN A LEPAK, F A C P , General Chairman, Twenty-sixth Annual Session, St Paul, Minn

CARL B DRAKE, President of the Ramsey County Medical Society

HERBERT Z GIFFIN, F A C P , President of the Minnesota Medical Association

HAROLD S DIEHL, Dean, University of Minnesota Medical School

The Honorable JOHN J McDONOUGH, Mayor of St Paul

The Honorable HAROLD E STASSEN, Governor of Minnesota

Response to Addresses of Welcome

ROGER I LEE, F A C P , President of the American College of Physicians

3 30 INTERMISSION

President Roger I Lee, F A C P , presiding

AVIATION MEDICINE

4 00 A Brief History of Aviation Medicine and the Physical Qualifications for Flying

LOUIS H BAUER, F A C P Consultant in Aviation Medicine and in Cardiology, Civil Aeronautics Administration, Hempstead, N Y

- 4 20 The Effects of High Speed Including Dive Bombing Aero Embolism
CAPTAIN JOHN R POPPEN, (MC), U S Navy, F A C P , Bureau of
Aeronautics, Navy Department, Washington, D C
- 4 40 Oxygen Want and the Use of Supplementary Oxygen
MAJOR HARRY G ARMSTRONG, (MC), U S Army, F A C P , Director of
Research, School of Aviation Medicine, Randolph Field, Tex
- 5 00 ADJOURNMENT

SECOND GENERAL SESSION

Monday Evening, April 20, 1942

Presiding Officer

James E Paullin, F A C P , Atlanta, Ga

p m

- 8 00 The Leaven of Psychosomatic Medicine
EDWARD A STRECKER, F A C P , Professor of Psychiatry, University of
Pennsylvania School of Medicine and Graduate School of Medicine,
Philadelphia, Pa
- 8 30 Is the Art of Physical Diagnosis Being Neglected in Modern Medical Educa-
tion?
G GILL RICHARDS, F A C P , Visiting Physician, Dr W H Groves
Latter-Day Saints Hospital, Salt Lake City, Utah
- 8 50 Specific Stimulating Substances in the Urine of Patients with Myelogenous
Leukemia
JOSEPH T WEARN, F A C P , Professor of Medicine, Western Reserve
University School of Medicine, Cleveland, Ohio
- 9.10 Leukemia The Relative Incidence of Its Various Forms, and Their Response
to Radiation Therapy
FRANK H BETHELL, F A C P , Assistant Professor of Internal Medicine,
University of Michigan Medical School, Ann Arbor, Mich
- 9 30 ADJOURNMENT

10 00 o'Clock

SMOKER

Stem Hall, Municipal Auditorium

A diverting and amusing program has been arranged See announcement under
"Special Features " Admission by registration badge

THIRD GENERAL SESSION

Tuesday Afternoon, April 21, 1942

Presiding Officer

D Sclater Lewis, F A C P , Montreal, P. Q

p m

- 2 00 The Use of Radioactive Elements in Biology and Medicine
WILLIAM J KERR, F A C P , Professor of Medicine,
JOHN H LAWRENCE (by invitation), Assistant Professor of Medi-
cine and Research Associate in the Radiation Laboratory,
JOSEPH G HAMILTON (by invitation), Clinical Instructor in Neurology
and Research Associate in the Radiation Laboratory.

(This paper is from the Department of Medicine, University of California Medical School, San Francisco, and the Crocker Radiation Laboratory, University of California, Berkeley, Calif)

- 2 45 Clinical Studies on the Prevention of Venous Thrombosis and Pulmonary Embolism by the Use of a Preparation from Spoiled Sweet Clover Which Prolongs Coagulation and Prothrombin Time of the Blood
EDGAR V ALLEN, F A C P , Associate Professor of Medicine, University of Minnesota (Mayo Foundation), Head of a Division of Medicine, Mayo Clinic, Rochester, Minn
N W BARKER, F A C P , Associate Professor of Medicine, University of Minnesota (Mayo Foundation), Consultant in Medicine, Mayo Clinic, Rochester, Minn
- 3 05 Embolism of the Popliteal Artery Its Diagnosis and Treatment
JOSEPH C DOANE, F A C P , Clinical Professor of Medicine, Temple University School of Medicine, Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine, Medical Director, Jewish Hospital, Philadelphia, Pa
- 3 25 The High Fluid Intake in the Management of Edema, Especially Cardiac Edema
F R SCHEMM, F A C P , Great Falls, Mont
- 3 45 INTERMISSION
- 4 05 Newer Knowledge Concerning the Effects of Kidney Extracts on Hypertensive Patients
IRVINE H PAGE (Associate, A C P), Director of Clinical Research, Eli Lilly and Company, Indianapolis, Ind
- 4 25 Circulatory Disturbances Associated with Prostatic Hypertrophy
MEREDITH MALLORY, F A C P , Chief of Medical Services,
FRED MATHERS, F A C P , Associate Attending Physician,
LOUIS M ORR, F A C S (by invitation), Chief of Urological Service, and
PALMER R KUNDERT, F A C S (by invitation), Urological Service, Orange General Hospital, Orlando, Fla
- 4 45 The Fraudulent Use of Digitalis to Simulate Heart Disease
O F HEDLEY, F A C P , U S Public Health Service, Bethesda, Md
- 5 00 ADJOURNMENT

FOURTH GENERAL SESSION

Wednesday Afternoon, April 22, 1942

Presiding Officer

Jonathan C Meakins, F A C P , Montreal, P Q

COMMUNICABLE DISEASES

p m

- 2 15 Poliomyelitis Virus and Flies
JOHN R PAUL (by invitation), Associate Professor of Medicine, Yale University School of Medicine, New Haven, Conn
- 2 35 A Comparison of Experimental Poliomyelitis in Several Varieties of Monkeys
JAMES D TRASK (by invitation), Associate Professor of Pediatrics, Yale University School of Medicine, New Haven, Conn
- 2 55 Typhus Fever
JOHN S SNIDER (by invitation), The Rockefeller Institute, International Health Foundation, New York, N Y

- 3 15 Newer Knowledge Concerning the Inception of Pneumonia and Its Bearing on Prevention
OSWALD H ROBERTSON (by invitation), Professor of Medicine, University of Chicago, The School of Medicine, Chicago, Ill
- 3 40 INTERMISSION
- 4 00 The Army's New Frontiers in Tropical Medicine
LT COL JAMES S SIMMONS, (MC), U S Army, F A C P , Chief, Division of Preventive Medicine, Office of the Surgeon General, Washington, D C
- 4 20 Considerations of the Malaria Problem on the Basis of Current Investigations
LOWELL T COGGESHALL (by invitation), Professor of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Mich
- 4 40 Resurvey of Underlying Factors in Tuberculosis
THEODORE L BADGER, F A C P , Instructor in Medicine, Harvard Medical School, Research Fellow, Thorndike Memorial Laboratories, Boston City Hospital, Boston, Mass
- 5 00 ADJOURNMENT

ANNUAL CONVOCATION

Wednesday Evening, April 22, 1942

8 30 o'Clock

Theater, St Paul Municipal Auditorium

All members of the profession and the general public are cordially invited No special admission tickets required

- 1 The President's Address
Roger I Lee
- 2 Presentation of Newly-elected Fellows and Recital of the Pledge
George Morris Piersol, Secretary-General
- 3 Presentation of the John Phillips Memorial Medal for 1941-42
- 4 Announcement of Research Fellows of the College for 1942
- 5 Convocational Address A Consideration of the Factor of Change in the Animal Organism
WILLIAM DEB MACNIDER, F A C P , Kenan Research Professor of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, N C

President's Reception

The Reception and Dance will follow one-half hour after the completion of this program and will be held in the Ballroom (mezzanine floor) of the Hotel Lowry. A cordial invitation is issued to all members and guests, with their families. Newly-inducted Fellows should sign the Roster and secure their Fellowship Certificate during the Reception at the Hotel Lowry.

FIFTH GENERAL SESSION

Thursday Afternoon, April 23, 1942

Presiding Officer

William D Stroud, F A C P , Philadelphia, Pa

p m

- 2 00 Definition of the Criteria of an Acceptable Operation for Ulcer
OWEN WANGENSTEEN (by invitation), Professor of Surgery, University of Minnesota Medical School, Minneapolis, Minn
- 2 20 Ileostomy for Chronic Ulcerative Colitis, an Analysis of Results in One Hundred Eighty-five Cases
J ARNOLD BARGEN, F A C P , Associate Professor of Medicine, University of Minnesota (Mayo Foundation) and Consultant in Medicine, Mayo Clinic, Rochester, Minn ,
W W LINDAHL (by invitation), Fellow in Medicine, Mayo Foundation, Rochester, Minn ,
FRANK ASHBURN (by invitation), Fellow in Surgery, Mayo Foundation, Rochester, Minn
- 2 40 Discussion of the Nature of the Hyperglycemia of the Obese Middle-Aged Person
L H NEWBURGH, F A C P , Professor of Clinical Investigation, University of Michigan Medical School, Ann Arbor, Mich
- 3 00 New Trends in Treatment of Chronic Disease, an Experience in Spa Therapy
WALTER S McCLELLAN (by invitation), Associate Professor of Medicine, Albany Medical College, Saratoga Springs, N Y
- 3 20 The Mediaeval Physician
JABEZ H ELLIOTT, F A C P , Professor of History of Medicine, University of Toronto Faculty of Medicine, Toronto, Ont
- 3 45 INTERMISSION
- 4 00 Pertinent Problems of Geriatric Medicine
EDWARD J STIEGLITZ, F A C P , Research Associate in Charge of Investigations in Gerontology, National Institute of Health, Washington, D C
- 4 20 Factors which May Influence Senescence
NATHAN S DAVIS, III, F A C P , Assistant Professor of Medicine, Northwestern University Medical School, Chicago, Ill
- 4 40 ADJOURNMENT, to be followed immediately by
THE ANNUAL BUSINESS MEETING

All Masters and Fellows are urged to be present Annual reports of the Secretary-General, Executive Secretary and Treasurer will be presented, new Officers, Regents and Governors will be elected, and the President-Elect, Dr James E Paullin, Atlanta, Ga , will be inducted into office

THE ANNUAL BANQUET OF THE COLLEGE

Thursday Evening, 8 00 o'Clock

Ballroom, Hotel Lowry

(Procure tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster John A Lepak, F A C P , St Paul, Minn

Address "Medicine and the Public"

William A O'Brien, Director of Postgraduate Medical Education, University of Minnesota, Minneapolis, Minn

SIXTH GENERAL SESSION

Friday Afternoon, April 24, 1942

Presiding Officer

George Morris Piersol, F A C P , Philadelphia, Pa

p m

- 2 15 The Clinical Significance of Pyuria
WILLIAM F BRAASCH (by invitation), Professor of Urology, University of Minnesota (Mayo Foundation), Rochester, Minn
- 2 35 Penicillin as a Chemo-therapeutic Agent
M HENRY DAWSON (by invitation), Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N Y
- 2 55 Gramicidin in the Treatment of Local Infections
CHESTER S KEEFER, F A C P , Wade Professor of Medicine, Boston University School of Medicine, Boston, Mass
- 3 15 Primary Coccidioidomycosis
WILLIAM A WINN (Associate, A C P), Superintendent and Medical Director, Tulare-Kings Counties Joint Tuberculosis Hospital, Springville, Calif , and
GILBERT JOHNSON (by invitation), Springville, Calif
- 3 35 The Effectiveness of Replacement Therapy in Achlorhydria
ALFRED E KOEHLER (Associate, A C P), Sansum Clinic, Santa Barbara, Calif
- 3 55 Ten Years' Experience with Thorotrast Hepatosplenography
WALLACE M YATER, F A C P , Professor of Medicine, Georgetown University School of Medicine, Washington, D C
- 4 10 A Recent Advance in the Treatment of Gout
ELMER C BARTELS, F A C P , Physician, New England Deaconess and New England Baptist Hospitals, Boston, Mass
- 4 30 ADJOURNMENT

GENERAL SESSIONS

IF TIME PERMITS

- Studies on Induced Auricular Fibrillation with Quinidine, Hydroquinidine, and "Pure Quinidine"
S A WEISMAN, F A C P , Clinical Assistant Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minn
- Observations on the Effects of Combined Fever and X-Ray Therapy in the Treatment of Malignancy
EDWARD L TURNER, F A C P , Dean and Professor of Medicine, Meharry Medical College, Nashville, Tenn ,
HIDDY S SHOULDERS (by invitation), Professor of Radiology, Meharry Medical College, Nashville, Tenn , and
LAWRENCE D SCOTT (by invitation), Assistant Professor of Radiology, Meharry Medical College, Nashville, Tenn
- Blood Pressure and Sulfocyanates
VFPNI S CAVINESS, F A C P , Assistant Chief of Medical Staff, Rex Hospital, Raleigh, N C ,
THOMAS L UMPHRETT (Associate, A C P), Attending Physician, Rex Hospital, Raleigh, N C , and

CHAUNCEY L ROYSTER (by invitation), Associate Physician, Rex Hospital,
Raleigh, N C

Potential Health Hazards in a Changing Social and Economic World

F GORHAM BRIGHAM, F A C P , Physician-in-Chief, Palmer Memorial and New
England Deaconess Hospitals, Boston, Mass

Medical Education after Graduation

HUGH J MORGAN, F A C P , Professor of Medicine, Vanderbilt University
School of Medicine, Nashville, Tenn

Orientation of Treatment in Thrombophlebitis, Phlebothrombosis and Pulmonary
Embolism

JAMES A EVANS, F A C P , Physician, Medical Department, Lahey Clinic,
Boston, Mass

MORNING LECTURES

The Morning Lectures are in response to increasing interest in fundamental
problems and are planned to relate as closely as possible to the subject matter of
the General Sessions

They will be held daily, Tuesday through Friday, from 9 30 to 11 30 a m , in
the Theater of the Municipal Auditorium

The lectures will be open to all members and guests of the College

Admission by regular registration badge

Tuesday, April 21, 1942

Theater, Municipal Auditorium

Presiding Officer

Thomas T Holt, F A C P , Wichita, Kan

a m

9 30-10 30 The Plans of the Army and Navy for Treatment of Shock
G CANBY ROBINSON (by invitation), Lecturer in Medicine and Lec-
turer in Preventive Medicine, Johns Hopkins University School
of Medicine, Baltimore, Md

10 30-11 30 Blood Proteins
EDWIN J COHN (by invitation), Professor of Biological Chemistry,
Harvard Medical School, Boston, Mass

Wednesday, April 22, 1942

Theater, Municipal Auditorium

Presiding Officer

Samuel E Munson, F A C P , Springfield, Ill

a m

9 30-10 30 The Male Hormones
ALLAN T KENYON (by invitation), Assistant Professor of Medicine,
University of Chicago, The School of Medicine, Chicago, Ill

10 30-11 30 The Female Hormones
ELMER L SEVRINGHAUS, F A C P , Professor of Medicine, University
of Wisconsin, Medical School, Madison, Wis

PROGRAM OF THE ST PAUL MEETING

Thursday, April 23, 1942

Theater, Municipal Auditorium

Presiding Officer

T Homer Coffen, F A C P , Portland, Ore

a m

9 30-10 30 The Use of Heat in Therapeutics

STAFFORD L WARREN (by invitation), Professor of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N Y

10 30-11 30 The Use of Cold in Medicine

LAWRENCE W SMITH (by invitation), Professor of Pathology, Temple University School of Medicine, Philadelphia, Pa

Friday, April 24, 1942

Theater, Municipal Auditorium

Presiding Officer

Gerald B Webb, F A C P , Colorado Springs, Colo

a m

9 30-10 30 Epilepsy

WILLIAM G LENNOX (by invitation), Assistant Professor of Neurology, Harvard Medical School, Boston, Mass

10 30-11 30 A Review of the Drastic Therapies of the Psychoses

FRANKLIN G EBAUGH (by invitation), Professor of Psychiatry, University of Colorado School of Medicine, Denver, Colo

PANEL DISCUSSIONS

The Panel Discussions embrace not only timely subjects, but also topics of the greatest interest and practical nature to the profession. Care has been taken to avoid too many duplications with topics discussed within recent years, yet where a subject has remained perennially fresh, it has not been omitted. Only highly qualified men in their respective fields have been chosen as leaders of the Panel Discussions and they in turn have selected their own personnel. For the most part the discussers have been gathered from all parts of the country in order to secure the best talent available for each Panel. In three instances, however, the chief of a department at the University of Minnesota, for the sake of better teamwork, preferred to take his own departmental associates, representing various phases of the subject, along into the Panel Discussion. Under such circumstances the listeners should be able to receive the latest as well as the most orthodox views and opinions on the subject under discussion.

The Panel Discussions will be held in the Municipal Auditorium from 12 00 m to 1 15 p m daily—Tuesday through Friday.

When application is made for tickets, it is suggested that the applicant submit in writing any question or phase of the subject which he especially wishes discussed. Questions may also be submitted at least twenty-four hours before the discussion to the General Chairman. A certain number of these request questions may not be answered on account of the lack of time. Leaders will answer those questions which seem to be most in demand.

Members should make application for Panel Tickets on the regular application form accompanying the formal program, or at the Registration Bureau at the Municipal Auditorium.

PANEL DISCUSSIONS—12 00 M-1 15 P M

	PANEL DISCUSSIONS—12 00 M-1 15 P M				
	PERIPHERAL VASCULAR DISEASES INCLUDING HYPERTENSION	HEMATOLOGY	ELECTROCARDIOGRAPHY	TRAUMATIC LESIONS OF THE CENTRAL NERVOUS SYSTEM	ACUTE AND CHRONIC TYPES OF ARTHRITIS
Tuesday April 21	*Edgar V Allen Irving S Wright I H Page	*H Z Giffin F J Heck F J Hirschboeck	*A R Barnes Harold Feil Edgar Hull Frank N Wilson	*Ernest M Hammes W H Hengstler George Ruhberg	*Philip S Hench Richard H Freyberg Russell L Cecil
Wednesday April 22	TREATMENT OF GLOMERULONEPHRITIS	GERIATRICS—THE MEDICAL PROBLEM OF OUR ADVANCING AGE GROUP	VITAMIN ADMINISTRATION IN PREVENTION AND TREATMENT OF DEFICIENCY DISEASES	PEDIATRICS AND CONTAGIOUS DISEASES	ORGANIC AND FUNCTIONAL DISORDERS OF THE UPPER DIGESTIVE TRACT, SMALL BOWEL AND COLON
	*Moses Barron Norman M Keith Louis Letter	*E L Tuohy W C Alvarez Edward J Stieglitz	*Russell M Wilder Hugh R Butt Norman Jolliffe	*Irvine McQuarrie E J Huenekens E S Platon	*George B Eusterman J B Carey E G Wakefield
Thursday April 23	THE ALLERGIC DISEASES	PRACTICAL USES OF ENDOCRINE SUBSTANCES	TUBERCULOSIS	CORONARY INSUFFICIENCY—DIAGNOSIS AND TREATMENT OF ANGINA PECTORIS AND CORONARY OCCLUSION	TREATMENT OF LOBAR PNEUMONIA
	*R V Ellis Elmer M Rusten Asher A White Albert V Stoesser	*Max Hoffman Elmer L Sevringhaus E H Ryncarson Willard O Thompson	*J A Myers C A Stewart S A Slater	*S Marx White Wm J Kerr Fred M Smith	*George E Fahr Jonathan C Meakins Francis G Blake
Friday April 24	HEART DISEASES	VIRUS DISEASES OF THE NERVOUS SYSTEM	DISEASES OF THE LIVER AND BILIARY TRACT	PROBLEMS CONCERNING THE CLINICAL USE OF SULTANILAMIDE AND RELATED COMPOUNDS	INDICATIONS AND CONTRA-INDICATIONS, OR USES AND ABUSES OF INTRAVENOUS THERAPY
	*Fredrick A Willius R Wesley Scott William D Stroud	*J C McKinley Robert Green A B Baker	*Cecil J Watson T L Althausen J L Bollman	*Wesley W Spink Alex E Brown Edwin G Bannick	*Henry L Ulrich Gerald Evans John Anderson

* Chairman

CLINICS AND DEMONSTRATIONS

9 00 to 11 30 a m.

Tuesday, Wednesday, Thursday and Friday

April 21-24, 1942

Clinics will be held in five St Paul hospitals and two amphitheaters in the Medical School of the University of Minnesota. Each clinical morning will begin promptly at 9 00 o'clock and end with equal promptness at 11 30 in order to allow plenty of time for those who wish to reach the Panel Discussions. To avoid congestion in some and a greatly reduced attendance in other hospitals, registration and tickets will be required for clinics. After each clinic ten minutes will be allowed for questions and answers. Daily clinics will be held in the following hospitals

<i>Name of Hospital</i>	<i>Capacity</i>
<i>University Hospital, University of Minnesota Medical School</i> 412 S E Delaware Ave , Minneapolis, Minn	
A-1 Todd Amphitheater	150
A-2 Medical Science Bldg , Amphitheater, Room 15	350
<i>Ancker Hospital</i> 495 Jefferson Ave , St Paul, Minn	
B-1 West Ward, First Floor	350
B-2 Auditorium	150
<i>St Luke's Hospital</i> 287 Smith Ave , St Paul, Minn	
C-1 Nurses' Auditorium	200
C-2 Nurses' Recreation Hall	100
<i>St Joseph's Hospital</i> 69 N Exchange St , St Paul, Minn	
D-1 Auditorium	200
D-2 New Lecture Hall	.. 200
<i>Charles T Miller Hospital, Inc</i> 125 W College Ave , St Paul, Minn	
E-1 Staff Meeting Hall	80
E-2 Nurses' Auditorium	100
<i>Bethesda Hospital</i> 559 Capitol Blvd , St Paul, Minn	
F Auditorium	150

Hospitals participating, but not holding clinics are

Children's Hospital, Inc , 311 Pleasant Ave , St Paul, Minn
 Gillette State Hospital for Crippled Children, 1003 Ivey Ave , St. Paul, Minn
 Midway Hospital, 1700 University Ave , St Paul, Minn
 Mounds Park Hospital, 200 Earl Ave , St Paul, Minn
 Northern Pacific Hospital, 1515 Charles Ave , St Paul, Minn
 St John's Hospital, 390 Mounds Blvd , St Paul, Minn

Each individual clinician will give the history of the patient he presents, demonstrate the physical findings, enumerate the laboratory data, arrive at his own diagnosis, outline the course of treatment and finally discuss the prognosis. In the time allotted, it is expected that the clinician will present at least two patients. Such a procedure should prove undeniably instructive, practical and clinical in nature.

For physicians not especially interested in clinics, but more absorbed in clinical-pathological correlation or the interpretation of certain laboratory findings and

procedures, there will be set aside each morning a delightful program at St Joseph's Hospital in the New Lecture Hall. The morning exercises will be divided into two parts. The first part will consist of a demonstration of unusual roentgen-ray pictures, discussion of eye grounds in various diseases illustrated by colored drawings, demonstration of a great variety of dermatological conditions with colored slides, and finally the evaluation of a blood sedimentation test as a part of the routine health examination of young adults. The second part will consist of a clinical-pathological conference. A case report will be forwarded to each clinician selected to lead the conference. This report will be analyzed by the clinician at the conference to establish the diagnosis. The diagnosis will, then, either be confirmed or disapproved by the pathologist. Reports of the case under discussion will also be furnished to the audience.

If any one wishes, however, to secure case histories for study before the conference, he may obtain them by notifying

HAROLD EDWARD RICHARDSON, M D ,
Chairman on Clinics,
1154 Lowry Medical Arts Bldg ,
St Paul, Minn

UNIVERSITY AND SAINT PAUL HOSPITALS

TRUE to its pioneering traditions, St Paul has led the way in Minnesota in the establishment of hospitals. First city in the state to have such an institution, St Paul today boasts twelve modern, well-equipped hospitals, five of which will be the scene of clinics to be conducted during the annual meeting of the American College of Physicians. Also participating will be the University of Minnesota Hospital in Minneapolis. All the hospitals conducting clinics are approved for standardization by the American College of Surgeons, approved for general internship by the American Medical Association, and are members of the American Hospital Association.

St Joseph's Hospital (Figure 1) It was 89 years ago—1853—that the Sisters of St Joseph of Carondelet, acting at the instigation of the then Bishop Cretin, founded St Joseph's Hospital. St Paul was then a wild frontier territory, inhabited by warring bands of Sioux and Chippewa Indians. A hospital was sorely needed when in the fall of 1853 construction was begun on the four-story stone building. A year later it was completed, becoming the first institution for the care of the sick and wounded in the Minnesota territory. One dollar a day was the charge at that time for the care of patients.

Most noteworthy and historic achievement in St Joseph's history occurred on September 24, 1886, when the first cholecystectomy ever done in America was performed by Dr Justus Ohage, Sr. The patient withstood the operation well and remained in good health for fifty years.



FIG 1 ST JOSEPH'S HOSPITAL

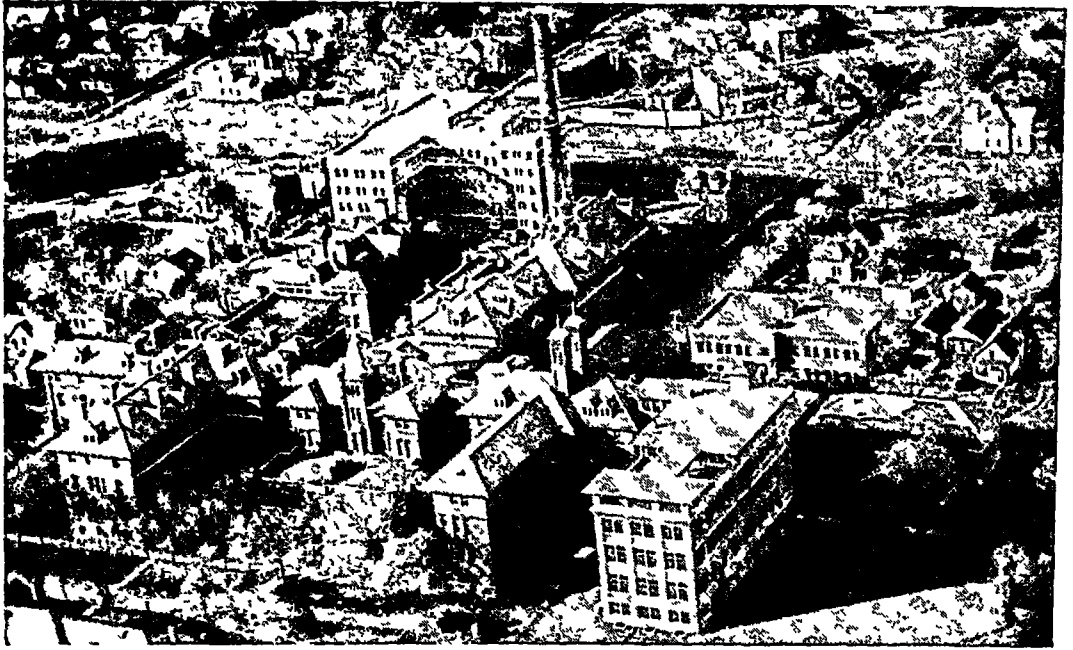


FIG 2 ANCKER HOSPITAL

Today St Joseph's is a modern general hospital with services in general medicine, general surgery, cancer, dermatology, diabetes, gynecology, some neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, pediatrics, some psychiatry, syphilis and urology. Contagious diseases and tuberculosis are not admissible cases. Special departments include a school of nursing, dietetic, roentgen-ray, clinical and pathological laboratories, physical therapy and electrocardiography. St Joseph's has 240 beds and 24 bassinets.

Ancker Hospital (Figure 2) Ancker Hospital, established in 1872 as the "City and County Hospital," had its name changed in 1923 in honor of Arthur B. Ancker, M.D., who served the institution from 1883 to 1923 as superintendent and physician and surgeon. The hospital is approved by the American College of Surgeons for graduate training in general surgery, urology, obstetrics and gynecology, ophthalmology and otolaryngology.

Owned by the City of St. Paul and Ramsey County, and controlled by a board of public welfare, Ancker Hospital provides services in general medicine, general surgery, cancer, contagious diseases, dermatology, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, pediatrics, psychiatry, syphilis, all stages of tuberculosis in any form, and urology.

Special departments at Ancker include outpatient, school of nursing, social service, dietetic, occupational therapy, electrocardiograph, postgraduate school of nursing, roentgen-ray, clinical and pathological laboratories. Capacity is 1,000 beds and 50 bassinets. Ancker is a teaching hospital affili-

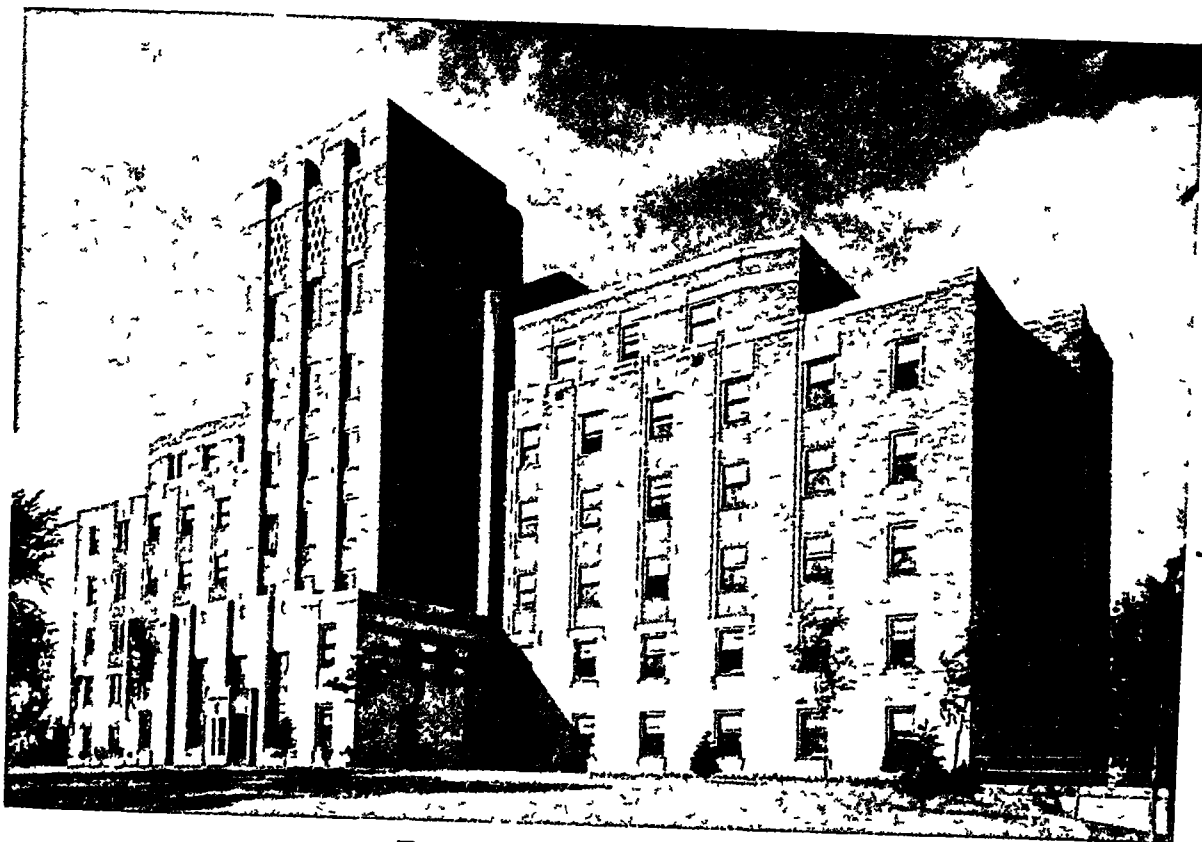


FIG 3 BETHESDA HOSPITAL

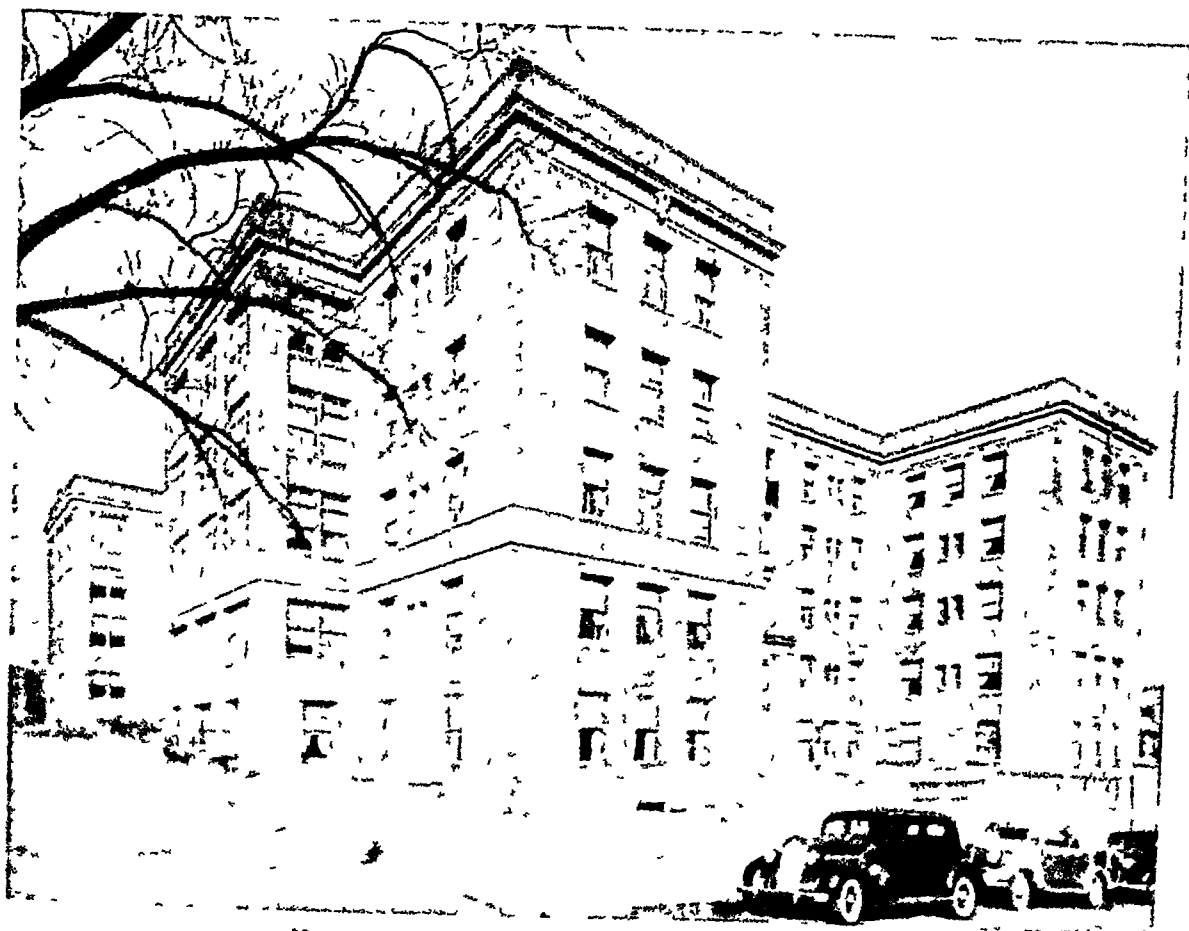


FIG 4 THE CHARLES T. MILLER HOSPITAL

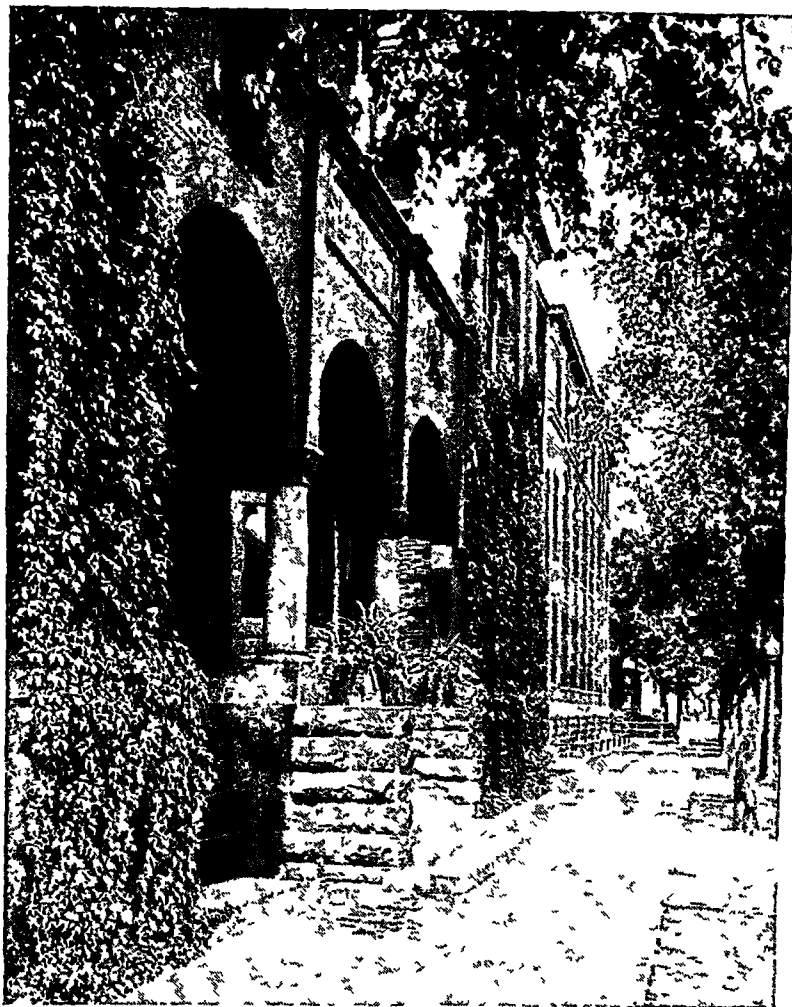


FIG 5 ST LUKE'S HOSPITAL

ated with the University of Minnesota Medical School. It is approved for general internship and residency in a specialty by the American Medical Association.

The hospital provides a rotating internship of one year's duration. The resident usually is selected from the intern group of the hospital. The plan of training in general surgery includes also orthopedic surgery and fractures. The first six months of training is in the department of pathology, with the next twelve devoted to orthopedic surgery and fractures. During the final eighteen months of training the resident has complete charge of the general surgical services.

Bethesda Hospital (Figure 3) St. Paul's newest, originally was founded fifty-nine years ago by the Lutheran Minnesota Conference of the Augusta Synod through the efforts of the Rev. A. P. Montan, pastor of the First Lutheran Church, St. Paul. It began in a private dwelling April 4, 1882, and continued for ten months, when it was discontinued for lack of

proper facilities In 1891 reorganization was instituted by the Conference and a year later the hospital reopened in a new location The present building, located behind the Minnesota State Capitol, was completed and dedicated October 2, 1932

A general hospital, Bethesda affords services in general medicine, general surgery, cancer, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, some pediatrics, syphilis, and urology Contagious and mental cases are not admitted Special departments are outpatient, school of nursing, dietetic, roentgen-ray, clinical and pathological labora-



FIG 6 UNIVERSITY OF MINNESOTA, MEDICAL CAMPUS, 1941

- | | | |
|---|------------------------------|-------------------------------------|
| 1 Medical Sciences Building | 14 Students' Health Service | 28 Hospital Administration |
| 2 College of Dentistry | 15 Interns Quarters | 29 Psychopathic Unit |
| 3 School of Medicine | 16 Child Psychiatry | 30 Surgery |
| 4 School of Nursing | 17 Obstetrics and Gynecology | 31 Neurosurgery |
| 5 Millard Hall | 18 Orthopedic Surgery | 32 Cancer Institute |
| 6 Preventive Medicine and Public Health | 19 Outpatient Department | 33 Radiation Therapy |
| 7 Department of Medicine | 20 Eustis Hospital | 34 Todd Memorial Hospital |
| 8 Physiology | 21 Pediatrics | 35 Internal Medicine |
| 9 Bacteriology and Immunology | 22 Diagnostic Roentgenology | 36 Ophthalmology and Otolaryngology |
| 10 Pharmacology | 23 Dermatology | 37 Louise M. Powell Hall for Nurses |
| 11 Institute of Anatomy | 24 Urology | 38 Pioneer Hall for Men |
| 12 Anatomy | 25 Anesthesiology | 39 Botany |
| 13 Pathology | 26 Elliot Memorial Hospital | 40 Zoology |
| | 27 Laboratory Service | |

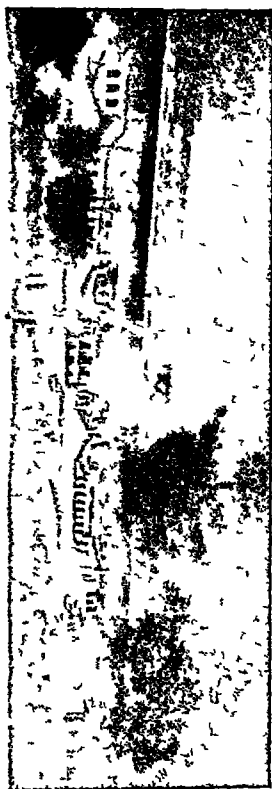


FIG 8 GILLETTE STATE HOSPITAL



FIG 10 MOUNDS PARK HOSPITAL

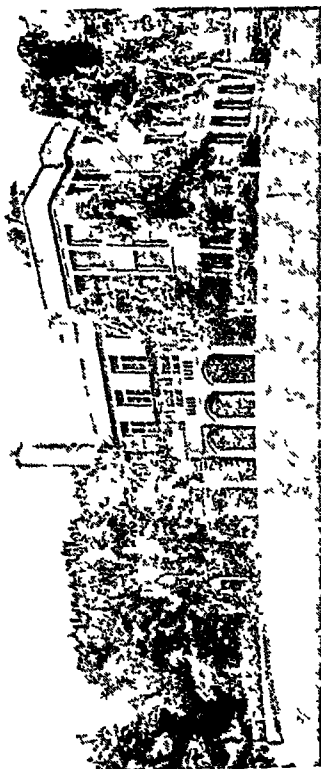


FIG 7 THE CHILDREN'S HOSPITAL

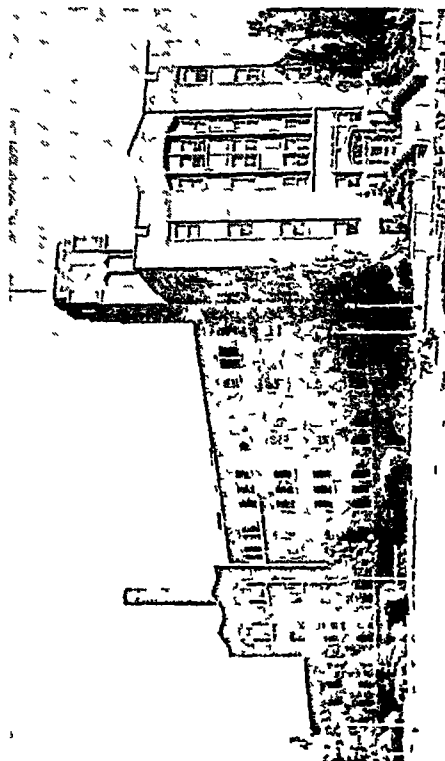
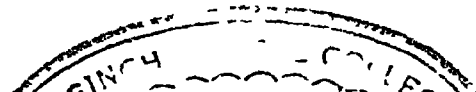


FIG 9 MIDWAY HOSPITAL



tories, physical therapy and electrocardiography Capacity, 110 beds, 14 bassinets

Miller Hospital (Figure 4) The Charles T Miller Hospital, a non-profit endowed institution, was opened December 1, 1920—the realization of the dreams and wishes of the late Charles Terry Miller, native of Jacksonville, Ill., who came to St Paul as a young man and acquired a fortune Mr Miller died in 1910 and his widow provided a bequest of \$1,400,000 to carry out her husband's wish to endow a hospital Her will stipulated that 50 free beds be maintained for indigent patients without regard to race, creed or color

Miller Hospital departments include outpatient, school of nursing, social service, dietetic, physical and occupational therapy, electrocardiography, post-graduate school of nursing, organized library, roentgen-ray, clinical and pathological laboratories

An outstanding feature of the hospital is its excellent diagnostic, chemical, serological and biological laboratory under the supervision of a full-time pathologist Through an affiliation with Macalester College, six students are received each year for training as laboratory technicians

In 1937 a specially constructed addition was built to house a 1,200 kilovolt roentgen-ray machine for deep therapy treatment This machine was built to yield radiation approaching the gamma rays of radium in penetration and quality It is one of the comparatively few installations in the country which produces such radiation

Since 1923 Miller Hospital has been affiliated with the Amheist H Wilder Dispensary, whose buildings adjoin the hospital The dispensary serves as the outpatient department of the hospital and is the source of the hospital's free patients

A general hospital, Miller's services include general medicine, general surgery, cancer, dermatology, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, pediatrics, syphilis, tuberculosis, and urology

St Luke's Hospital (Figure 5) Like St Joseph's Hospital, St Luke's was founded before Minnesota was admitted to the Union—in 1857 It was opened originally as an Episcopalian institution under the name, "Christ Church Hospital and Orphan Home for Minnesota" Its present name dates from 1877 The late General Henry Hastings Sibley, noted pioneer territorial delegate to Congress and governor when Minnesota was admitted to the Union, served as president of the hospital board from 1873 until his death in 1890

St. Luke's Hospital provides services in general medicine, general surgery, cancer, dermatology, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, syphilis, and urology Mental and contagious cases are not admissible Departments school of nursing,



FIG 11 NORTHERN PACIFIC HOSPITAL

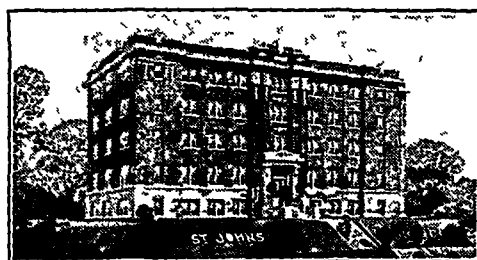


FIG 12 ST JOHN'S HOSPITAL



FIG 13 WEST SIDE GENERAL HOSPITAL

diabetic, physical therapy, electrocardiography, organized library, and roentgen-ray, clinical and pathological laboratories

University Hospital (Figure 6) The Minnesota General Hospital (University of Minnesota Medical Center), as its name implies, provides general services in medicine, surgery, cancer, dermatology, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, pediatrics, tuberculosis (surgery only), and urology. Contagious and mental diseases and active tuberculosis cases are not admitted.

University Hospital, as the institution is commonly known, was erected in 1911 through the generosity of Adolphus S. Elliot, M.D., and until 1921 was known as Elliot Memorial Hospital as a part of the University of Minnesota. In addition to Elliot Hospital, the University Medical Center comprises the Todd Hospital for the care of eye, ear, nose and throat cases, Eustis Hospital for children and the Memorial Cancer Institute.

The Mayo brothers, William J. and Charles H., both now deceased, played an important part in the development of the University of Minnesota Medical School and the University Hospitals. On February 9, 1915, they founded the Mayo Foundation for Medical Education and Research, entering into an agreement by the terms of which the funds and income of the foundation are devoted, under direction of the University Board of Regents, to the promotion of graduate work in medicine and to research in this field. On September 13, 1917, funds and income of the Mayo Foundation were transferred entirely to the Regents of the University.

Under terms of a Minnesota statute any legal resident of the state "afflicted with a malady, deformity or ailment of a nature which can probably be remedied by hospital service and treatment, and is unable financially to pay for same, is entitled to admission to the 'Minnesota General Hospital'." Public officials refer probable patients to the hospital and if necessary blanks are filled out, and county commissioners have given their approval, admission is granted. The hospital prefers needy patients with "teaching value."

Other St. Paul hospitals, in addition to those in which clinics are to be conducted, are Children's Hospital (Figure 7), Gillette State Hospital (Figure 8), Midway Hospital (Figure 9), Mounds Park Hospital (Figure 10), Northern Pacific Hospital (Figure 11), St. John's Hospital (Figure 12), and the West Side General Hospital (Figure 13).

ANNALS OF INTERNAL MEDICINE

VOLUME 16

MARCH, 1942

NUMBER 3

EXOPHTHALMOMETRIC MEASUREMENTS IN PATIENTS WITH THYROID DISEASES WITH SOME DISCUSSION OF THEIR SIGNIFICANCE*

By CARLOS GALLI-MAININI, M D,† *Buenos Aires, Argentina*

THE whole problem of the ophthalmopathy of Graves' disease of the classic and special varieties¹ has aroused much interest of late in this clinic. In order to get a comprehensive view of the degree of proptosis in various stages and types of the disease, actual exophthalmometric measurements have been made in 126 consecutive thyroid cases attending the Thyroid Clinic. The findings in these, and their significance, form the subject of this report.

METHOD

A modification, or elaboration of the Luedde‡ exophthalmometer was employed (figure 1). Actually, two of these instruments, attached parallel to each other, were joined at right angles to the ends of two pieces of brass tubing, one of which could be telescoped into the other. Thus the exophthalmometers could be separated or approximated by sliding the tubing and at the same time kept in their parallel relationship. The notched end of each instrument is fitted to the bony angle of the outer margin of either orbit, the whole held in place by digital pressure on the brass connecting piece. Readings are taken in the usual way for the instrument. The advantage of the double device is that error due to varying inclination of the line of measurement is avoided.

* Received for publication October 30, 1941.

From the Thyroid Clinic of the Massachusetts General Hospital, Boston.

† Research Fellow, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts. Formerly from Ramos Mejia Hospital, Buenos Aires, Argentina.

I wish to thank Dr. J. H. Means for the facilities he has given me in his laboratory and for his supervision of my work.

‡ Manufactured by the E. B. Meyrowitz Company, New York City.

Copyright, 1942, by The American College of Physicians

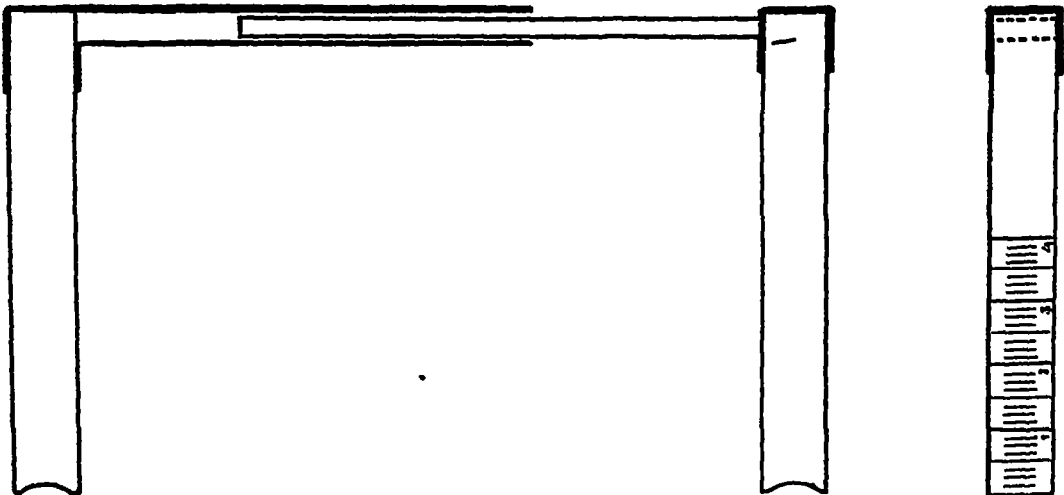


FIG 1 The modified Luedde exophthalmometer

CLINICAL MATERIAL

The results of measurements in the 126 cases are all shown in figures 2 and 3. It will be understood that the present study is in the nature of a

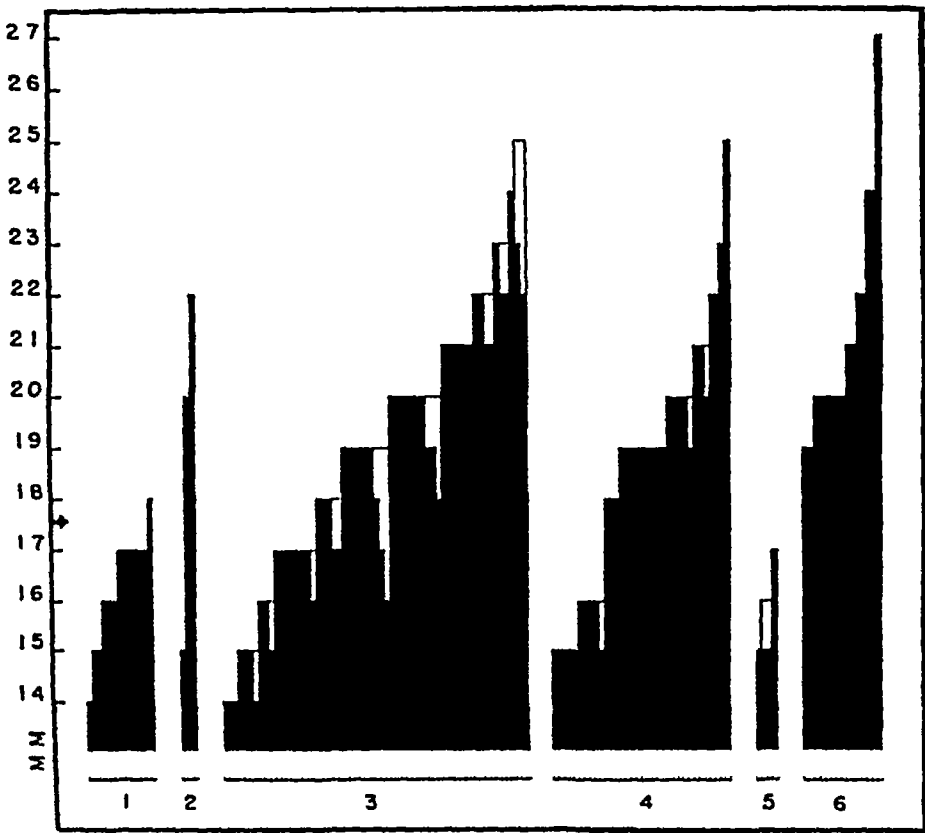


FIG 2 The degree of proptosis in millimeters in patients is represented by the height of the columns. Group 1 Non-toxic nodular goiter. Group 2 Toxic nodular goiter. Group 3 Hyperthyroidism with diffuse enlargement of the gland. Group 4 Spontaneous myxedema. Group 5 Myxedema after surgery without exophthalmos during the course of the thyrotoxicosis. Group 6 Myxedema after surgery with exophthalmos during the course of the thyrotoxicosis.

static survey of a wide field, or cross section of a mass of unselected thyroid material as seen in the clinic, rather than a dynamic study of the progress of exophthalmos in selected cases. In figure 2 the heights of the columns represent the measurements of protrusion in millimeters. When the two eyes had the same degree of protrusion the measurement is represented by a column in full black. When the protrusion was asymmetric the smaller is shown in black, the larger in white.

As a normal control the eyes of 50 healthy persons were measured and the readings all fell between 14 and 17.5 millimeters. Any measurement over the latter figure is, therefore, considered to be exophthalmos. This is indicated by an arrow in figure 2.

The thyroid cases are arranged in figure 2 in groups as follows:

1. Thirteen patients with non-toxic nodular goiter, giving no past history of exophthalmos and not appearing to have it at the time of examination, five of whom had previously been operated upon and eight others who had no operation. The measurements ran from 14 to 18 millimeters. Only one was above the higher range of normal.

2. Three patients with toxic nodular goiter, two of whom gave the history of exophthalmos in the past and appeared to have it at time of examination, and one with no such history or appearance. Their measurements ran from 15 to 22 millimeters, one normal, two exophthalmic.

3. Fifty-eight thyrotoxic patients with diffuse goiters, 40 of whom gave a history of exophthalmos, and all of whom appeared to have it at the time of examination. Their measurements ran from 18 to 25 millimeters. That is to say, all were above normal.

4. Thirty-four cases of spontaneous myxedema, all of whom had ceased taking thyroid for at least a week. The one showing the greatest protrusion had never had thyroid therapy. None of this group gave a history of exophthalmos, nor did any of them appear exophthalmic on inspection, but the actual measurements of their eyes ran from 15 to 25 millimeters, 21 of them, in fact, had definite exophthalmos by measure.

5. Four cases of myxedema following thyroidectomies for toxic goiter without exophthalmos. Their eye measurements were all within normal limits.

6. Fourteen cases of myxedema following thyroidectomy for toxic goiter with exophthalmos. All 14 showed exophthalmos at time of measurement, from 19 to 27 millimeters.

The largest measurement obtained, 27 millimeters, fell in this group.

The group of thyrotoxicosis and diffuse goiter (classic Graves' disease), group 3 in figure 2, was next broken down to discover the effect of time elapsing since the patient had the disease, the effect of iodine alone in treatment, and of iodine followed by surgery or roentgen irradiation.

The subgroupings of group 3 are shown in figure 3 as follows:

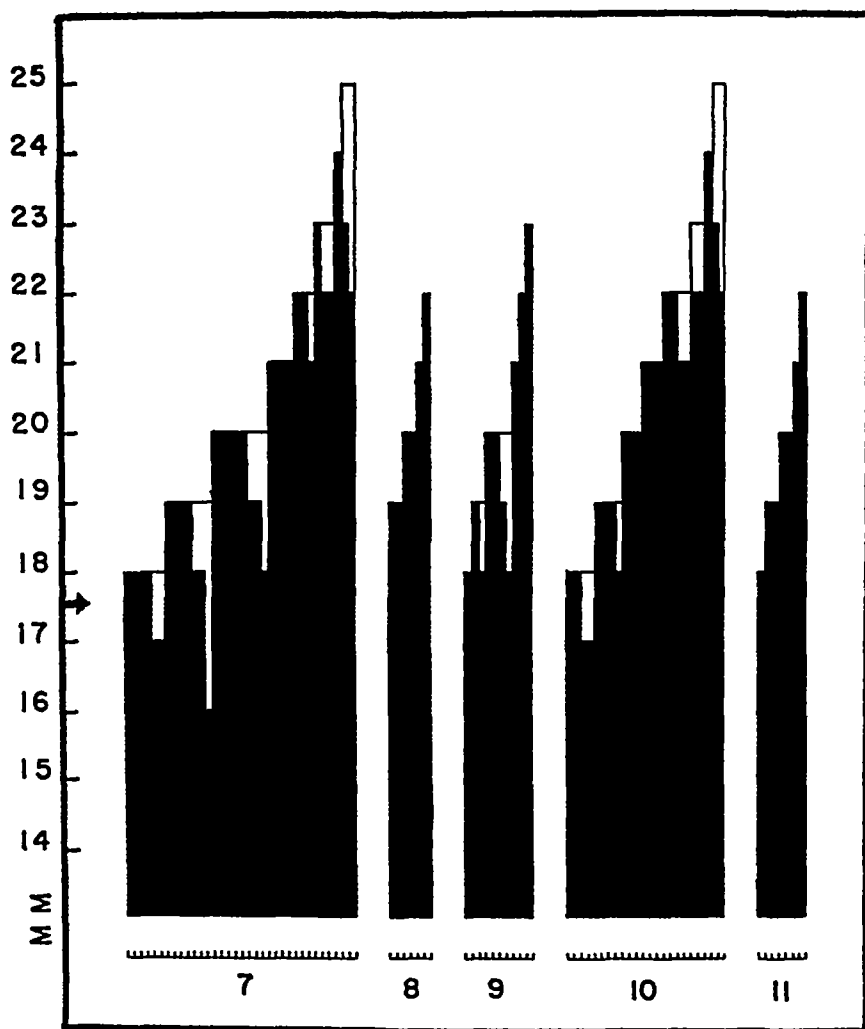


FIG 3 Subgroup of Group 3 of figure 2 (hyperthyroidism with diffuse enlargement of the gland) *Group 7*, Thyrotoxic patients who had had the disease more than 1 year before the measurements were taken *Group 8*, Thyrotoxic patients who had had the disease within the year when the measurements were taken *Group 9*, Thyrotoxic patients treated with iodine alone *Group 10*, Thyrotoxic patients treated with iodine followed by surgery or roentgen-ray treatment *Group 11*, Patients who had received the same treatment but who had had the disease within the year when the measurements were taken

7 Thirty-four patients who had the disease more than one year before the measurements were made Their measurements ran from 18 to 25 millimeters

8 Six patients who had had the disease less than one year before the measurements were made Their measurements ran from 19 to 22 millimeters

9 Ten patients treated by iodine alone Their measurements ran from 18 to 23 millimeters

10 Twenty-four patients who were treated by iodine followed by operation more than one year before the measurements were made Their measurements ran from 18 to 25 millimeters

11 Seven with the same treatment as group 10 but less than one year before the measurements were made Their measurements ran from 18 to 22 millimeters

DISCUSSION

It appears from the results obtained that exophthalmos in Graves' disease is a condition which, when acquired, is never completely recovered from. From the present studies one cannot say that after treatment there is any change from previous conditions. It can be said, however, that in 100 per cent of those patients who were recognized as having exophthalmos during the active phase of the disease, some degree of this condition was persisting at the time thereafter when our measurements were made.

Of our 42 patients with thyrotoxicosis and exophthalmos (40 with diffuse and two with nodular glands), three had had the disease six years before the measurements were made, two had had it seven years before, one had had it eight years before, three had had it nine years before, one had had it 11 years before, three had had it 12 years before, three had had it 14 years before, two had had it 15 years before, two had had it 16 years before, one had had it 18 years before, one had had it 20 years before, and one had had it 24 years before. Even after these long periods of time patients showed measurable exophthalmos. Furthermore, as brought out in figure 3, it appears that neither duration nor type of treatment for the Graves' disease abolishes altogether the exophthalmos. Some degree of it persists if ever it has been present.

In the case of myxedema, exophthalmos was not noted clinically, but when measurements were taken it was proved to be present. It probably was not recognized on inspection because the puffiness of the surrounding tissues obscured the protrusion, and because such related eye signs as stare and lid retraction were lacking.

It may be now permissible to attempt an explanation of the findings. The weight of evidence available—clinical, anatomic, and experimental—indicates that edema of the intraorbital tissues, connective tissues and fat, as well as of the muscles, plays an important rôle in the genesis of the exophthalmos of human Graves' disease. The muscles, furthermore, in some cases, are the seat of lymphocytic infiltration and degeneration of their fibers.

Certain experimental work^{2, 3, 4, 5, 6} seems to indicate that excess of thyrotropic hormone may be responsible for exophthalmos in animals. Indeed, as long ago as 1910 Gley⁷ demonstrated that exophthalmos may follow thyroidectomy in rabbits and dogs, and in discussion of his paper Poncet⁷ offered the interpretation that this effect might be due to overactivity of the pituitary. The inference has, therefore, been drawn that this hormone is responsible for the exophthalmos of human Graves' disease, and indeed it cannot be gainsaid that, in some cases, it may play a part. However, that it is the whole cause of exophthalmos in all cases of human Graves' disease, is most unlikely. Undoubtedly there are other factors operating as well. The theory of thyrotropic hormone causation of exophthalmos would imply that all cases of Graves' disease with exophthalmos

are due to stimulation by the pituitary, and contrariwise that those without exophthalmos are not so caused. But such is not in accord with the facts. For example, by present methods^{8,9} it cannot be shown that there is any excess of thyrotropic activity in the blood or urine of patients with classic Graves' disease. Furthermore, in acromegaly, in which an excess of thyrotropic activity can be fairly regularly demonstrated, there may or may not be exophthalmos. In the special type of Graves' disease, described in previous papers from this clinic,¹ there is an excess of thyrotropic activity in the blood and urine as in acromegaly^{9,10}

Furthermore, it is difficult to understand how a humoral agent like a hormone which bathes all tissues could produce edema in one set of muscles and one lot of fat and connective tissue without involving other muscles, connective and fat tissue of the body.

It seems to the writer that the explanation of localized edema in a general disturbance such as thyrotoxicosis should be sought in the special anatomic characteristics of the orbit and its contents, which would make these tissues react in a different way from similar tissues in the remainder of the body.

The eyeball fits the orbit somewhat as a cork does a bottle, and it is maintained in position by the action of two pressures working in opposite directions. One of these is the pressure exerted by the tension of muscles, which tends to pull the eyeball backward, the other is the tissue pressure of the orbital contents, which tends to push the eyeball forward. The two are in such balance in health as to maintain a constant volume of orbital content, and at the same time to secure normal movement of the globes and circulation of the orbit.

That an intra-orbital tissue pressure actually exists can be proved by taking tonometric readings as is done for measuring any tissue pressure.¹¹ That the position of the eye is determined by the relative magnitude of the opposing pressures is indicated by the following facts: (1) In cases in which it may be inferred that tissue pressure drops, as in loss of intra-orbital fat or water from starvation or dehydration, enophthalmos develops. (2) In cases in which it may be inferred that tissue pressure rises, as in intraorbital tumors, exophthalmos develops. (3) When muscular tension is diminished as in paralysis of the ocular motor nerves, exophthalmos is produced.

The mechanism of production of edema in general has been studied by many authors, and the factors involved seem to be essentially the following:

1. Increased intracapillary pressure. This may result from either increased arterial or venous pressure.

2. Decreased osmotic pressure of the blood. This may be due mainly to low protein content.

3. Dilatation of capillaries. Hudach and McMaster¹² showed that an increased extravasation of dye occurs in the rabbit's ear when the ear is exposed to heat which causes capillary dilatation.

4 Increased capillary permeability

5 Diminished tissue pressure in tissues traversed by capillaries This factor produces a passage of fluid across the capillary wall until accumulation of it in the tissues causes a rise of pressure which prevents further extravasation

Factors 1, 2, 3 and 4 can be shown to exist in thyrotoxicosis Concerning factor 1, it is known that an increase of pulse pressure is found in this disease Concerning factor 2, it has been shown by Brown and Mecray¹³ that in 15 out of 24 thyrotoxic patients there was a serum protein level lower than that of normal persons Also Bartels¹⁴ got similar results in 43 cases and says, "This deviation of serum-protein content from normal may have physiological effects on the body as a whole It may be responsible for the edema in cases of hyperthyroidism that is not caused by cardiac or renal insufficiency" In his studies Bartels shows that 63 per cent of patients had total serum protein values below the lowest level of the normal range and the serum albumin content was below normal in 73 per cent of the cases

Concerning factor 3, Roberts and Griffith,¹⁵ studying the cutaneous capillaries in thyrotoxic patients, showed that "most of the cutaneous capillaries are open"

Concerning factor 4, White and Jones¹⁶ have shown that patients with thyrotoxicosis tend to have rates of filtration from capillaries in the upper range of normal Of this finding they say, "Wide dilatation of the capillary bed produces an increase in the available surface of capillary endothelium"

Bartlett¹⁷ states that in hyperthyroidism there is a tendency to water retention which causes pulmonary and cerebral edema in some cases He also considers that the "arteriolarization" of the venous blood, demonstrated by Gladstone¹⁸ in such cases, is a collateral factor in the production of edema

From all these facts it seems probable that in hyperthyroidism there is a tendency to the production of edema We may say, perhaps, that while at a thyrotoxic level the organism is being maintained at the upper limit of its water regulating capacity, gross edema does not occur because of the diuretic action of thyroid hormone present in excess When thyrotoxicosis is abolished, however, as by thyroidectomy, there is a rapid retention of water due to the cessation of diuretic action of thyroid hormone, while the water retaining factors are still in action, included among these may be an unopposed action of thyrotropic hormone

The explanation of edema in the orbit may be found in the simultaneous action of the edematogenic factors already mentioned, on the one hand, and to decreased pressure of orbital tissues upon their capillaries, on the other hand This decrease in tissue pressure may be brought about through relaxation of the extra-ocular muscles, occasioned by the weakness which

besets them in thyrotoxicosis, along with other muscles of the body. It is well known that a more or less generalized myasthenia is a feature of thyrotoxicosis. In this myasthenia the extra-ocular muscles are probably involved. Several signs of myasthenia may be apparent. Often only muscular weakness, but in extreme cases actual atrophy may be evident.¹⁹ The process may involve the eye muscles so as to produce a genuine exophthalmic ophthalmoplegia.²⁰ The frequent sign of poor convergence may be taken to be evidence of participation of the eye muscles in the general myasthenia. Adler²¹ found that 24 of our 33 thyrotoxic persons showed positive reactions for myasthenia gravis.

The extrinsic muscles of the eye differ from others in that one point of their insertion is attached to bone and the other to a freely movable object, the eyeball. Weakness or paralysis of these muscles will permit the eyeball to move forward, due to unopposed intra-orbital tissue pressure. For example, Dixon²² says, "Proptosis (unilateral) may also result from paralysis of the external ocular muscles. This is seen in some cases of myasthenia gravis—though as a rule the proptosis in this condition is bilateral. The increased degree of force necessary to replace the eye in the first and subsequent examinations must be due to an increase in the fluid content of the orbit." And among other patients he describes two with unilateral exophthalmos, probably due to thyrotoxicosis with palsy of the third, fourth and sixth nerves and one due to early progressive muscular atrophy with palsy of the third and fourth.

As has been said above, it is the tension of the extra-ocular muscles which maintains the pressure inside the orbit. Relaxation of the muscles causes a diminution in tissue pressure and, as a result of this diminution in pressure, all of the five edematogenic factors enumerated above are present simultaneously in the orbit. These are increased capillary pressure, decreased osmotic pressure, capillary dilation, probably increased capillary permeability—these being local manifestations of a generalized process—and in addition drop in orbital tissue pressure which is the result of the local starvation of the orbit.

As a result of the excess of fluid that had passed from the capillaries to the tissues, the pressure rises and prevents further extravasation of fluid. At this moment an equilibrium of tensions and pressures within the orbit will again have been achieved, but with this difference from the normal state, that the contents of the orbit will have increased in volume owing to the extra fluid added to it, and the eyeball will be occupying a more forward position.

When these events have occurred, other changes may take place in the orbit, if the edema be considerable. The muscles may degenerate and become infiltrated with lymphocytes. An obstacle to venous return, from pressure of edema on veins, may develop which can aggravate the picture and produce the type of progressive exophthalmos with marked edema of the eyelids and edema and injection of the conjunctivae.

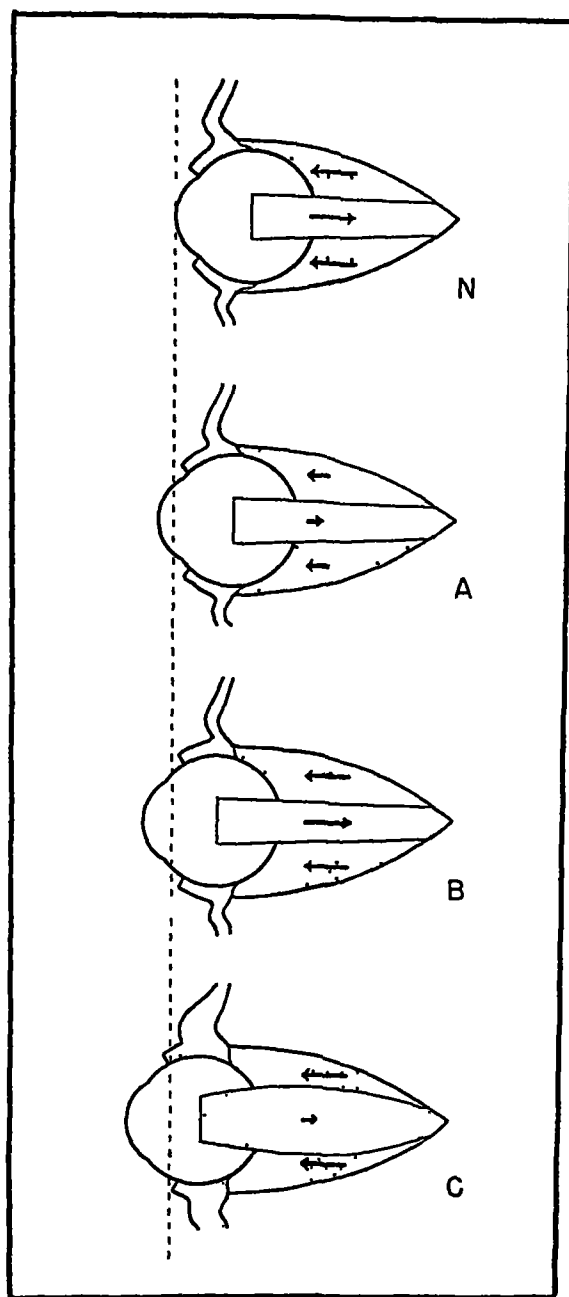


FIG 4 Schemata representing the mechanism involved in the production of exophthalmos. The lids, the eyeball, one muscle and the intra-orbital tissue are represented. The arrows indicate the direction of pressures and tensions. The dots represent the amount of fluid in the tissues. In Schema N is shown the situation in health. The pull of the muscle is of the same magnitude as the tissue pressure and balances it, so that the position of the globe is that found in normal persons, indicated in these schemata by the interrupted line. Schema A shows the first step in the development of exophthalmos. The muscle has weakened, exerts less tension, indicated by the shortened arrow. The tissue pressure therefore forces the eyeball forward. As this happens tissue pressure falls and fluid passes from capillaries to tissue to occupy the space, until a new equilibrium is reached with the muscles stretched and the eyeball protruding—Schema B. In Schema C is shown the situation in progressive exophthalmos in which a weakened and degenerate muscle cannot withstand the tissue pressure and in its turn becomes edematous as do the lids and surrounding tissues.

The magnitude of the various factors will determine the degree of exophthalmos. Soley²³ has shown that exophthalmos progresses after operation in a considerable percentage of the cases. This can be ascribed to a retention of water during the postoperative period. Some of the most severe cases of exophthalmos appear in patients who have had generalized edema during the course of the disease. Certain of the patients seen in the Thyroid Clinic of the Massachusetts General Hospital have shown improvement in their exophthalmos under the influence of restricted fluid and salt, and the administration of diuretics. There was improvement but no complete cure. The eyes did not return to a totally normal position. Long-standing edema can produce irreversible changes in the form of fibrosis—compare, for example, the brawny edema of the legs in chronic heart disease, from which total recovery would be impossible. Also, if we consider that the extra-ocular muscles are themselves edematous, infiltrated and degenerated, it is easy to understand their incapacity ever to return to their normal length, which would be necessary to the complete evacuation of extra water from the orbit.

The explanation of exophthalmos in spontaneous myxedema may be similar, namely that such patients retain water unduly, and also have weak muscles. Other diseases in which there is water retention may be accompanied by exophthalmos, as chronic nephritis²⁴ or hypertension, or in experimental chronic renal insufficiency as shown by Marine²⁵.

The exophthalmos produced in myxedematous animals by injections of thyrotropic hormone may be explained on the same basis, namely that this hormone through its water-storing action aggravates the edema already present. In the intact organism, the thyrotropic hormone may lead to exophthalmos by two mechanisms, one producing hyperthyroidism and the other causing water retention. The impossibility of producing exophthalmos by the administration of thyroid in the normal animal can be explained by loss of fat and dehydration of the orbit. As a matter of fact exophthalmos can take place in animals which have lost weight rapidly and intensely, and exophthalmic animals can be benefited by the injection of thyroxin as well as by starvation or dehydration.

SUMMARY

In this paper are presented measurements of the degree of protrusion of the eyes in 126 patients seen in the Thyroid Clinic, 13 of whom had non-toxic nodular goiters, 3 had thyrotoxicosis with nodular goiter, 58 had thyrotoxicosis with diffuse goiter, 18 had myxedema following surgery to the thyroid and 34 had spontaneous myxedema.

Exophthalmometric measurements were made with a modified Luedde exophthalmometer. For control the eyes of 50 normal persons were measured. The upper limit of protrusion in these normals was found to be 17.5

millimeters Therefore in patients any measurement greater than this was considered to be exophthalmos

In all of those patients who had been recognized to have had exophthalmos during the active phase of their disease, some degree of it was persisting at the time thereafter when measurements were made

Patients who had no history of exophthalmos during the course of their disease gave measurements within normal limits when examined by the author

The usual forms of treatment for Graves' disease, whether iodine alone or followed by surgery or roentgen irradiation, seem incapable of completely abolishing exophthalmos

Of 34 patients with spontaneous myxedema, 21 had exophthalmos by measure

The thyrotropic hormone is considered not the sole factor in the production of exophthalmos, but rather one among several

There are some reasons for supposing that in thyrotoxicosis there is a tendency toward the production of edema, and that the organism is maintained at the upper limit of its water regulating capacity Gross edema may not occur because of the diuretic action of thyroid hormone in excess

In the production of edema in the orbit, it is believed that the extraocular muscles play an important rôle Under conditions of health they, through the tension they exert, maintain a certain intra-orbital tissue pressure which is necessary to normal circulation in the orbit In thyrotoxicosis, due to the weakness of the muscles which accompanies it, there is a drop in orbital tissue pressure which permits the escape of fluid from the vessels This state of affairs also is aggravated by other edematogenic factors which are present, namely, increased pulse pressure, decreased osmotic pressure, dilatation of capillaries and increased capillary permeability

REFERENCES

- 1 HERTZ, S, MEANS, J H, and WILLIAMS, R H Graves disease with dissociation of thyrotoxicosis and ophthalmopathy, *West Jr Surg, Obst and Gynec*, 1941, xlix, 493-498
- 2 FRIEDGOOD, H B Experimental exophthalmos and hyperthyroidism in guinea-pigs, *Bull Johns Hopkins Hosp*, 1934, liv, 48-67
- 3 LOEB, L, and FRIEDMAN, H Exophthalmos produced by injections of acid extract of anterior pituitary gland of cattle, *Proc Soc Exper Biol and Med*, 1932, xlix, 648-650
- 4 MARINE, D, and ROSEN, S H Exophthalmos in thyroidectomized guinea-pigs by thyrotropic substance of anterior pituitary and the mechanism involved, *Proc Soc Exper Biol and Med*, 1933, xxx, 901-903
- 5 PAULSON, D L Experimental exophthalmos and muscle degeneration induced by thyrotropic hormone, *Proc Staff Meet Mayo Clin*, 1939, xiv, 828-832
- 6 SMELSER, G K The histology of orbital and other fat tissue deposits in animals with experimentally produced exophthalmos, *Am Jr Path*, 1939, xv, 341-352
- 7 GLEY, E De l'exophtalmie consecutive a la thyroïdectomie presentation d'animaux, *Compt. rend Soc. de biol*, 1910, lxxviii, 858-862

- 8 HERTZ, S, and OASTLER, E G Assay of blood and urine for thyrotropic hormone in thyrotoxicosis and myxedema, *Endocrinology*, 1936, xx, 520-525
- 9 GALLI-MAININI, C Effect of the serum of patients with Graves' disease, myxedema and acromegaly upon the oxygen consumption (QO_2) of guinea pig thyroid, *Endocrinology*, 1942, xxx, 166-170
- 10 HERTZ, S Personal communication
- 11 HENDERSON, Y, OUGHTERSON, A W, GREENBERG, L A, and SFARLE, C P Muscle tonus, intramuscular pressure and the menopressor mechanism, *Am Jr Physiol*, 1935-36, cxiv, 261-268
- 12 HUDACH, S, and McMASTLR, P D The gradient of permeability of the skin vessels as influenced by heat, cold and light, *Jr Exper Med*, 1932, lv, 431-439
- 13 BROWN, R B, and MECRAY, P M Serum proteins before and after operations for hyperthyroidism, *Endocrinology*, 1938, xlii, 303-306
- 14 BARTELS, E C Serum protein studies in hyperthyroidism, *New England Jr Med*, 1938, ccxviii, 289-294
- 15 ROBERTS, E, and GRIFFITH, J Q A quantitative study of cutaneous capillaries in hyperthyroidism, *Am Heart Jr*, 1937, xiv, 598-602
- 16 WHITE, B V, and JONES, C M The rate of filtration through the capillary walls as measured by the pressure plethysmograph Observations on control subjects, and on patients with intrahepatic disease, thyrotoxicosis and myxedema, *Jr Clin Invest*, 1937, xvi, 73-80
- 17 BARTLETT, W The hydration of hyperthyroid patients and its relationship to edema, especially cerebral, *Surg, Gynec and Obst*, 1940, lxxi, 450-453
- 18 GLADSTONL, S A Oxygen utilization, cardiac output, and related circulatory functions in Graves' disease, *Proc Soc Exper Biol and Med*, 1936, xxxiv, 587-591
- 19 MORGAN, H J, and WILLIAMS, R H Muscular atrophy and weakness in thyrotoxicosis (thyrotoxic myopathy exophthalmic ophthalmoplegia), *South Med Jr*, 1940, xxxiii, 261-269
- 20 BRAIN, W R, and TURNBULL, H N Exophthalmic ophthalmoplegia, *Quart Jr Med*, 1938, vii, 293-323
- 21 ADLER, H Thymusfunktion bei Myasthenie, Myotonie und Morbus Basedow, *Arch f klin Chir*, 1938, xciii, 743-748
- 22 DIXON, J Unilateral exophthalmos (proptosis) causation and differential diagnosis, *Brain*, 1941, lxiv, 73-89
- 23 SOLLY, M H In press
- 24 BARKER, L F, and HANLS, F M Quoted by Marine
- 25 MARINI, D Studies on the pathological physiology of the exophthalmos of Graves' disease, *Ann Int Med*, 1938, vii, 443-453

DIGITALIS IN THE PREVENTION OF RECURRENT CARDIAC FAILURE IN PATIENTS WITH SINUS RHYTHM *

By M SOKOLOW, M D , *San Francisco, California*, H B WEINBERG, M D ,
Davenport, Iowa, J L PLAUT, M D , and L N KATZ, M D ,
Chicago, Illinois

ALTHOUGH digitalis is one of the oldest drugs used in specific cardiac therapy, and probably the most widely used, there is still some dispute as to its indications and value under various circumstances. Opinions range from those recommending that digitalis be administered in all cases of heart disease (Christian,¹ Cloetta²) to those stating that digitalis has striking value only in cases of auricular fibrillation, and here only by slowing the ventricular rate (Lewis³). That digitalis slows the ventricular rate in auricular fibrillation has been conclusively demonstrated (Mackenzie,⁴ Cushny⁴). This may improve the efficiency of the heart and produce striking relief of symptoms. In patients with sinus rhythm, however, some still question the indications for digitalis administration (Lewis,⁶ Cotton⁷). Recent observations indicate that this drug is effective in relieving congestive heart failure in a certain percentage of patients with sinus rhythm (Pratt,⁸ Christian,⁹ Luten,¹⁰ Marvin,¹¹ Harrison, Calhoun, and Turley,¹² and Gravey and Parkinson¹³).

We have been interested in a different aspect of this problem, viz., whether digitalis will, in an ambulatory patient who has recovered from cardiac failure, prevent a recurrence of the failure. Gold and DeGraff¹⁴ have shown that in auricular fibrillation digitalis must be continuously maintained to prevent recurrences of the failure. In these cases it may operate in part at least by preventing excessive elevation of the ventricular rate under the diurnal stresses which the patient may encounter, as shown by Weinstein, Plaut and Katz¹⁵. Many textbooks (Harrison,¹⁶ Fishbein,¹⁷ White,¹⁸ Luten¹⁹) carry the statement, admittedly empirical, that digitalis should be of value in preventing cardiac failure in patients with regular rhythm. This is in accordance with widespread clinical opinion. We are not aware, however, that any objective data have been presented in support of this concept. It is this concept that we have attempted to study in an objective manner.

METHODS

Four patients who had previously shown cardiac failure with a regular rhythm and who had regained compensation on the usual therapy (bed rest,

* Received for publication September 21, 1940

From the Cardiovascular Department, Michael Reese Hospital, Chicago

Aided by the A. D. Nast Fund for Cardiac Research and the A. B. Kuppenheimer Fund

fluid restriction, salt restriction, diuretics, and digitalis) were under observation for a period varying from 31 to 60 weeks. Three patients had hypertensive heart disease and the fourth had arteriosclerotic heart disease. All were ambulatory throughout the period of study (with one exception who during a period of failure was hospitalized), and were kept on a comparable régime of activity, salt, fluid and caloric intake, the only controlled variable was the administration or omission of digitalis, and, when advisable to relieve heart failure, the intravenous administration of a mercurial diuretic. The powdered leaf was the preparation used. No fixed dosage was employed, the drug being given so that digitalization was accomplished in a week; this usually required 0.3 gm daily for seven days. The dose was then maintained at a level of 0.1 to 0.2 gm daily. After a control period of observation on maintenance dosage, the digitalis was omitted and the patient observed for subjective and objective evidence of cardiac failure. Upon the appearance of heart failure the patient was treated with whatever measures were necessary to restore compensation, after which the same routine was repeated. The period of intensive therapy to alleviate well-marked congestive failure never extended over more than two weeks, and was always followed by a suitable control period on digitalis alone before this drug was again omitted. Two periods of withdrawal of the drug were observed in two patients and three periods in the other two patients. Patients were excluded from the study who during the course of observation failed to report regularly, were unreliable, or developed conditions known to precipitate cardiac failure (acute infections, myocardial infarction, pulmonary infarction, thyrotoxicosis, etc.). No case was excluded because of inconsistency of response to digitalis withdrawal.

The patients were seen fortnightly as a rule, and were questioned and examined for clinical evidences of heart failure. In addition to this the following objective tests of circulatory status were performed on each visit under comparable conditions after a preliminary rest period: vital capacity, venous pressure, response of venous pressure to compression of the right upper quadrant of the abdomen, and circulation time. The vital capacity was determined in the sitting position, using a McKesson-Scott bellows type of instrument which was checked against a water spirometer. The best of three efforts was taken as the correct reading. Venous pressure was determined by the direct method, using a simple instrument which we constructed ourselves. This consists of a Kaufman-Luer syringe to the sidearm of which a 35 cm length of glass tubing of similar diameter and bore was connected by means of a 1-inch piece of rigid rubber tubing, producing in effect a 36 cm sidearm. This sidearm was completely filled with sterile 3 per cent sodium citrate solution, an 18-gauge needle inserted into an antecubital vein, and the plunger withdrawn until just beyond the orifice of the sidearm. The citrate solution in the tube was allowed to drop until it reached a stationary level. Ten centimeters above the table top was taken as the zero

level (Lyons, Kennedy and Burwell²⁰), and the difference between these two levels was read as the venous pressure. In every case we also noted the effect on the venous pressure of compression of the right upper quadrant of the abdomen for one minute (Oppenheimer and Hitzig²¹). Using the same needle, 3 to 5 c c of a 20 per cent calcium gluconate solution * were injected as rapidly as possible, the time of injection averaging approximately 14 seconds. The time from the beginning of injection until the first appearance of a sensation of warmth in the mouth or throat was recorded by a stop-watch. This test was always repeated 60 seconds after all sensation of warmth had disappeared, and the average of the two tests taken as the arm-to-tongue circulation time. In each patient the amount of solution injected was always the same. The patients were weighed at each visit under comparable conditions. The resting pulse and respiration were recorded on all visits, and the immediate and delayed (two minutes) effect of a standard exercise, which consisted of 10 round trips on a three-step platform, was observed.

RESULTS

Our results are shown in chart form in figures 1 to 4. Vital capacity determinations were not followed in one patient (P. B.) because this patient, although very cooperative, could not seem to master the technic required for this test. The venous pressure is expressed in centimeters of water. Rise on right upper quadrant pressure represents the increment when this maneuver was performed, and is expressed in millimeters of water. In no patient did we find any consistent significant variations in the respiratory rate, which we have, accordingly, omitted from the graphs. As a rule, we found variable correlation in the pulse rate, both resting and on standard exercise. These changes have been indicated in the case of one patient (figure 1), and in the other three similar results were obtained. The solid line connects the resting pulse rates at the various visits. The broken lines at each visit represent the pulse rate immediately after and two minutes after the standard exercise. The degree of failure represents our clinical estimation of this status on each visit, using 0 as the absence of all signs and symptoms and ++++ as the most severe degree of failure. The solid bars at the top of the figures indicate the period during which digitalis was being withheld. The remainder of the figures are self-explanatory.

Patient 1 (R. C.), whose chief symptom was dyspnea on exertion, reported aggravation of this symptom upon withdrawal of digitalis. This was manifested objectively in a very decisive manner by a reduction in his vital capacity (figure 1), and at a later stage and to a lesser degree by the appearance of basal râles. His circulation time also tended to become prolonged during these periods, but varied in a less consistent manner than did his vital capacity. His venous pressure showed very little variation. However, a rise in venous pressure on right upper quadrant compression did appear upon withdrawal of the drug, this phenomenon tended to precede or

* Kindly supplied by Sandoz Co

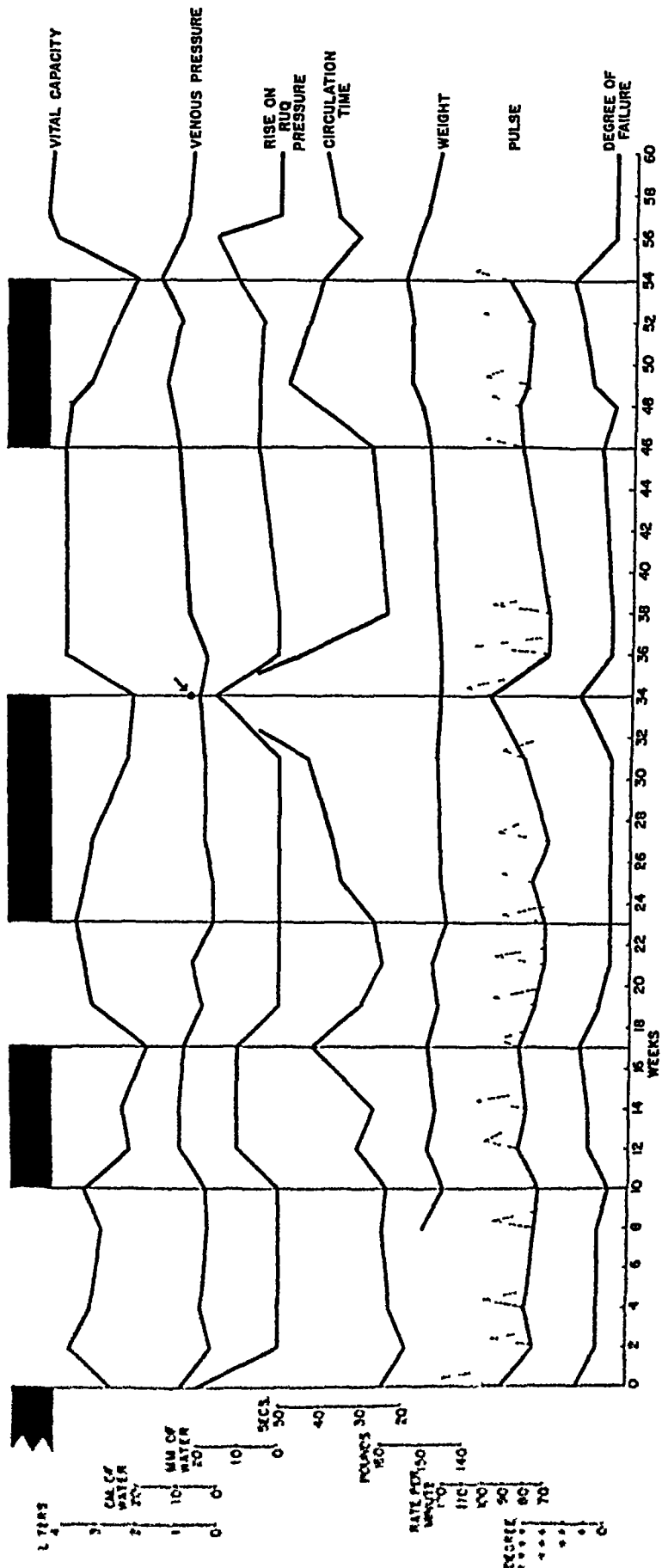


FIG 1

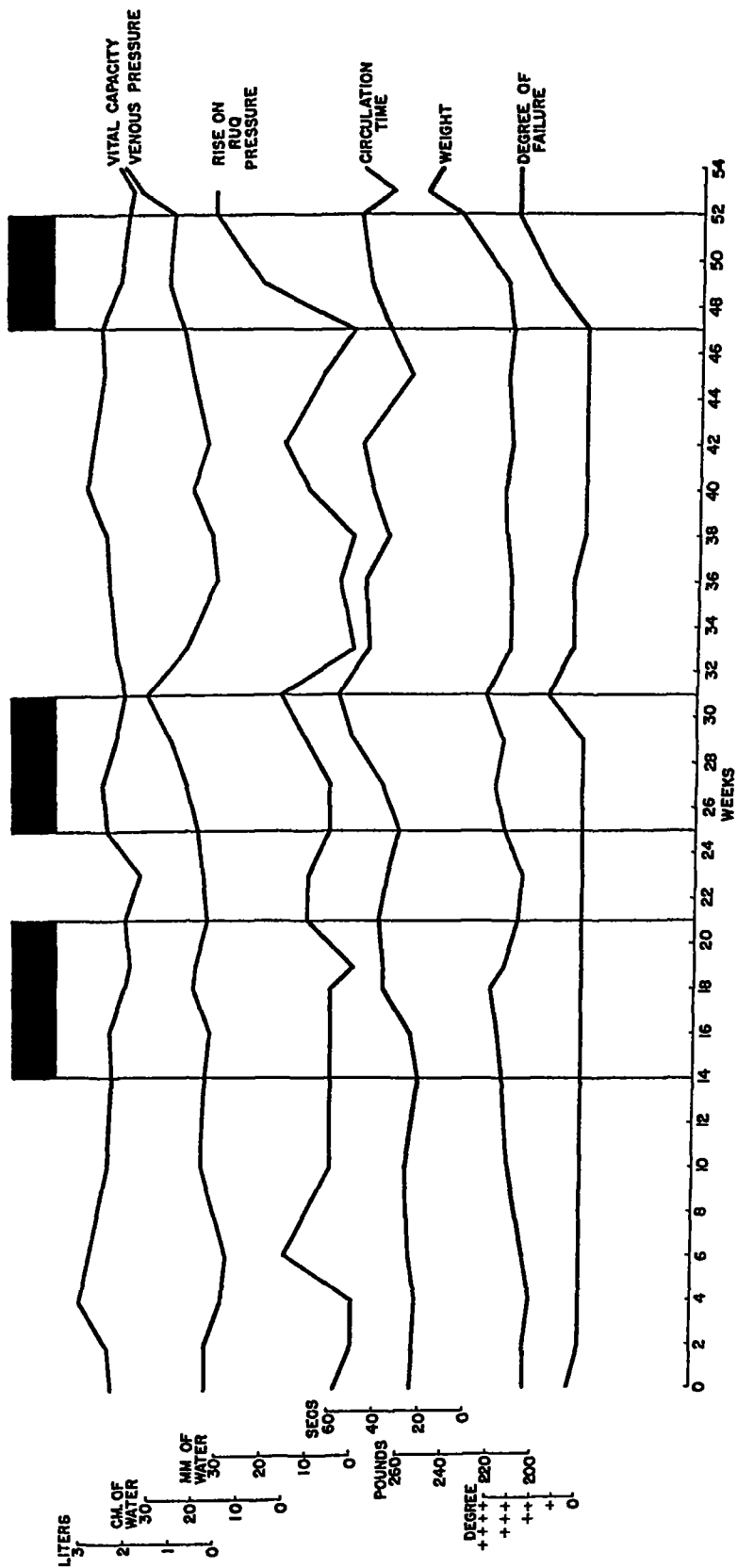


Fig 2

coincide with clinical evidence of liver engorgement. Neither the resting pulse rate nor the response of pulse to standard exercise showed a consistency of response to which we could attach any value. We found this latter to be true in all of our cases, and have, therefore, omitted it in the other three charts.

In patient 2 (H M) no single procedure mirrored his changing circulatory status as remarkably as did the vital capacity in the first patient (figure 2). During his first period of digitalis withdrawal, the vital capacity was decreased and the circulation time prolonged, but there was no significant change in venous pressure nor did clinically observable signs of cardiac failure appear. During the second period of withdrawal all observations changed concurrently, and definite congestive failure appeared. During the third period all observations showed a trend in the same direction, the most marked change occurring in the response of venous pressure to right

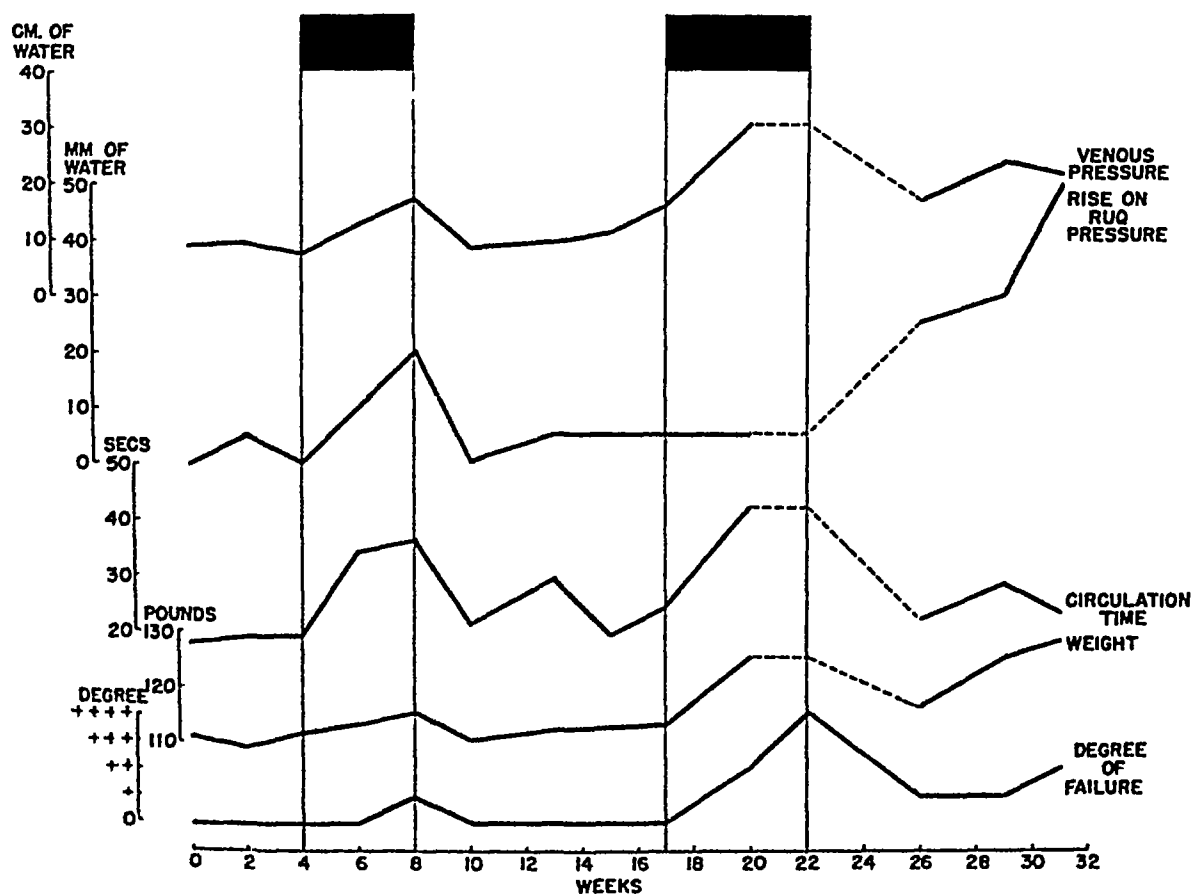


FIG 3

upper quadrant compression. After this time digitalis, as well as all other therapy, was of no avail, the patient dying in the hospital in severe congestive failure.

Patient 3 (P B) was followed through two periods of digitalis omission. During the first, clinical signs of failure of a slight degree developed, but the venous pressure and especially the circulation time showed earlier and more marked changes (figure 3). During the second, definite changes occurred in venous pressure, circulation time, and clinical status. It was on this occasion that hospitalization became necessary. Cardiac compensation was not completely restored and this patient thereafter developed progressive cardiac failure despite digitalis administration. Later, even though she was hospitalized and given intensive therapy, she died in the hospital 38 weeks after the beginning of the study. Her weight tended to correspond with the degree of clinical

failure, probably more nearly so than did any other observation. It is noteworthy that after her second period of digitalis withdrawal, her circulation times were not elevated to a degree corresponding to her venous pressure, clinical signs and weight. On her last out-patient visit, when the venous pressure was 22 cm and rose 50 mm on right upper quadrant pressure, the circulation time was only 23 seconds, a reading which was checked three times because of the apparent inconsistency, all three readings being within the range of 22 to 24 seconds.

Patient 4 (R T) went out of town twice during the study. In each instance he was taking digitalis when he left, and continued to do so until his supply ran out. He returned to the out-patient department, once three weeks after and once four days after discontinuing the drug and on each occasion reported that he had felt perfectly well.

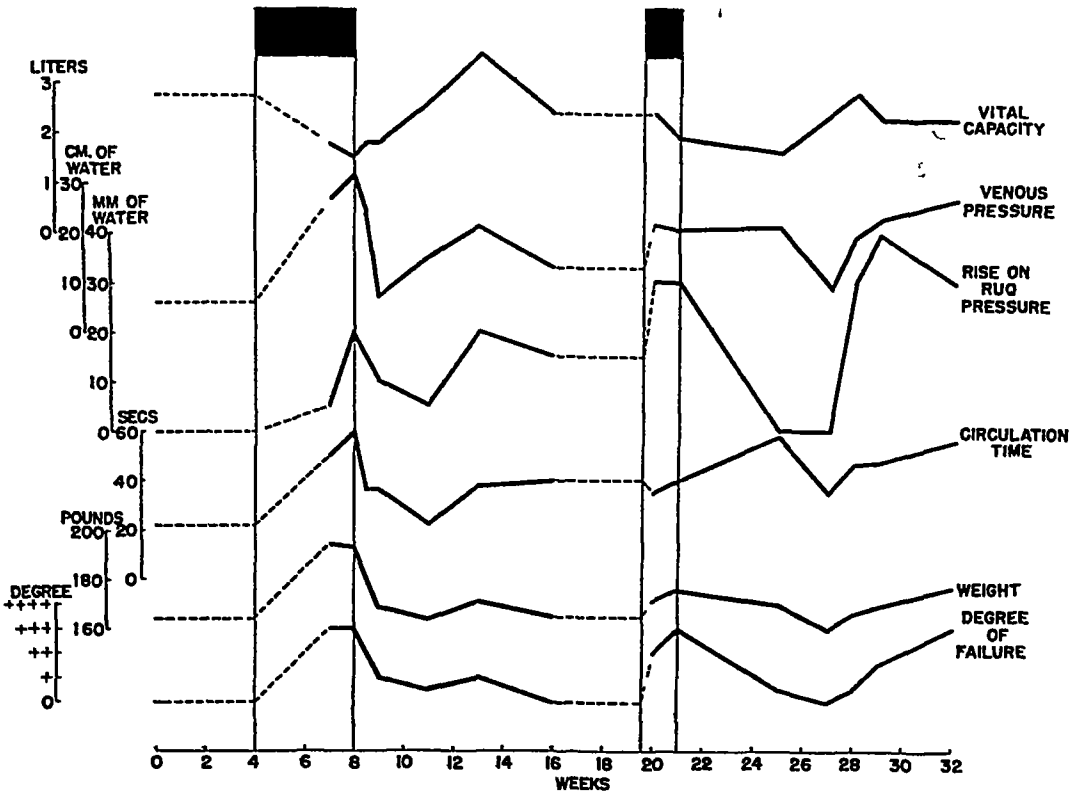


FIG 4

until he stopped the digitalis. In his case the vital capacity, venous pressure, circulation time, weight, and clinical degree of failure all tended to run roughly parallel (figure 4). However, some discrepancies among the various observations were noted between the twenty-fourth and twenty-eighth weeks of the study. At this same time his cardiac reserve had become so diminished that failure progressed in spite of full digitalization. Shortly after the completion of the study this patient entered the hospital, where his condition could not be improved beyond Class IV functional capacity (New York Heart Association²²).

In treating the congestive failure which followed the third period of digitalis withdrawal in H M (figure 2), the second in P B (figure 3), and both first and second in R T (figure 4) mercurial diuretics were used in addition to digitalis. The maximum quantity used was 4 c c over a period of two weeks.

DISCUSSION

In every instance signs of cardiac failure appeared following withdrawal of digitalis. The consistency of this occurrence indicates that the relationship is one of cause and effect, and not that of coincidence. The evidence herein presented offers strong objective support to the current impression that digitalis is of value in the prevention of recurrent cardiac failure in patients with sinus rhythm. We found, however, that as the cardiac reserve of a patient diminished, a stage was finally reached (patients 2, 3, 4) where digitalis was no longer effective in preventing the development of congestive failure. The serious outcome when this supervened—two patients died, and the third is left in an irreversible Class IV functional capacity—suggests, even from such a small series, that when a patient who previously responded fails to respond to digitalis therapy, the prognosis is grave. One must, of course, eliminate infections, thyrotoxicosis, etc., which diminish responsiveness to digitalis.

Although not the direct object of the study, our data suggest that digitalis also has value in restoring compensation in patients with sinus rhythm when cardiac failure had occurred. Thus, in six of the ten instances in which signs of failure developed upon digitalis withdrawal the resumption of digitalis administration produced a recession of these signs to the point of restoration of compensation. The four remaining instances do not negate this finding, because the mercurial diuretics were started simultaneously with the digitalis, and were not given as a final resort after digitalis had been tried alone. We administered both together at these times because we deemed it advisable to alleviate the patients' congestive failure as speedily as possible. Our evidence regarding the efficacy of digitalis in alleviating congestive heart failure in patients with sinus rhythm conforms to that presented by other investigators,^{5, 9, 10, 11, 12, 13} adding only the concept that this action may be produced in ambulatory patients. We must point out, however, that in those instances in which digitalis alone relieved the cardiac failure, the latter was of relatively mild degree. We have no evidence regarding the comparative value of digitalis relative to other measures which might have been used, nor do we have evidence that digitalis alone can alleviate a severe degree of congestive failure in these ambulatory patients.

We did not attempt to study the mode of action of digitalis. This is itself a disputed question (Harrison,¹⁶ Peters and Visscher,²⁰ Katz et al.,²¹ Stewart et al.,² Gold and Cattell²⁶). Nothing in our data casts any light upon this problem, and our results are compatible with the opinions of any of these investigators.

The repeated fortnightly observations over a period of months, as the patients were developing and recovering from cardiac failure, offered an excellent opportunity to evaluate the various circulatory tests employed. Our experience indicates that no single test was uniformly consistent in reflecting the earliest circulatory changes, although the combined data proved

satisfactory in following the changes in circulatory status. The response of venous pressure to right upper quadrant compression showed changes in patient 1 in the absence of marked changes in the venous pressure itself, but at times in the other patients its results were at variance with those of the other tests. In patient 3 it is notable that the circulation time in the latter weeks showed relatively little change in comparison with the other findings indicating failure of the heart. In patient 1 the reverse is true, the circulation time being prolonged in the latter weeks out of proportion to the other findings. The discrepancy in time relationship of the changes occurring between the twenty-fifth and twenty-eighth weeks in patient 4 has also been previously mentioned. We heartily recommend the use of these various tests in studies of this type in which objective data which can be presented and evaluated are desired, and a trend rather than a single determination is sought. In routine clinical practice, however, their value should be more limited because only seldom does one gain information from them that cannot be obtained from careful anamnesis and examination of the patient. Nor would we advise that the status of the circulatory system be judged by the results of any one of the tests at any one time—in our hands, at least, the results have not proved sufficiently reliable. The various tests which we have used require training in their performance and are just as subject to personal interpretation as is the simple clinical examination. When used, they should be correlated with all other available data. Each of these tests is subject to other variations in cardiovascular dynamics besides heart failure, and hence cannot be used as a sole measure of the presence or degree of heart failure. Nevertheless, our assembled data show clearly that a trend toward congestive failure occurred each time digitalis was withdrawn.

A complication such as acute infection, myocardial infarction, thyrotoxicosis, etc., may precipitate heart failure in a patient whose cardiac reserve has previously been unimpaired. It is also possible that recovery from such an episode may be so complete that the cardiac status may return approximately to its previous level. All of our patients, however, had developed congestive failure in the natural course of their disease, indicating that the reserve of their hearts had become markedly diminished. It does not follow from the evidence we obtained that digitalis should prove of prophylactic value in patients with little reduction in cardiac reserve, the objective procedure used in this study is not suitable to determine the value of digitalis in patients in whom cardiac failure is not so imminent. The use of this drug in the latter type of patient is still a matter of empirical judgment.

SUMMARY AND CONCLUSIONS

1 Four ambulatory patients with sinus rhythm, who had previously shown congestive heart failure, were studied for periods varying from 31 to 60 weeks. Each was kept on a comparable controlled regime of activity,

salt, fluid, and caloric intake The only variable was the administration or omission of digitalis

2 In every instance cardiac failure recurred when digitalis was withdrawn We conclude, therefore, that the administration of digitalis tends to prevent the development of failure in patients with sinus rhythm Digitalis also proved to be of value in relieving the congestive failure produced in these ambulatory patients by withdrawal of this drug

3 In three patients the cardiac reserve finally became so diminished that irreversible cardiac failure occurred in spite of all therapy

4 The objective measurements of vital capacity, venous pressure, response of venous pressure to right upper quadrant compression, circulation time, and weight, when correlated with the clinical findings, proved to be of value in following the trend of the circulatory status

5 Continuous digitalization is of value in preventing recurrences of cardiac failure in ambulatory patients with sinus rhythm It is unwise to omit this drug in patients with diminished cardiac reserve who have previously shown failure, even though the patient is free of symptoms

BIBLIOGRAPHY

- 1 CHRISTIAN, H A Use of digitalis other than in treatment of cardiac decompensation, *Jt Am Med Assoc*, 1933, c, 789-792
- 2 CLOETTA, M Biochemical action of digitalis, *Jr Am Med Assoc*, 1929, xciii, 1462-1466
- 3 LEWIS, T On cardinal principles in cardiological practice, *Brit Med Jr*, 1919, ii, 621-625
- 4 CUSHNY, A R Digitalis and its allies, 1925, Longmans, Green & Co, London
- 5 MACKENZIE, J Digitalis, *Heart*, 1910, ii, 273
- 6 LEWIS, T Diseases of the heart, 1937, 2nd edition, Macmillan Company, New York
- 7 COTTON, T F Modern methods in diagnosis and treatment of heart disease, *Canad Med Assoc Jr*, 1926, xvi, 487-492
- 8 PRATT, J H Digitalis therapy, *Jr Am Med Assoc*, 1918, lxxi, 618-622
- 9 CHRISTIAN, H A Digitalis therapy, *Am Jr Med Sci*, 1919, clvii, 593-602
- 10 LUTRN, D Clinical studies of digitalis, effects produced by administration of massive dosage to patients with normal mechanism, *Arch Int Med*, 1924, xxxiii, 251-278
- 11 MARVIN, H M Digitalis and diuretics in heart failure with regular rhythm, with especial reference to importance of etiologic classification of heart disease, *Jr Clin Invest*, 1927, iii, 521-539
- 12 HARRISON, T R, CALHOUN, J A, and TURLEY, F C Congestive heart failure, effect of digitalis on dyspnea and on ventilation of ambulatory patients with regular cardiac rhythm, *Arch Int Med*, 1931, xlviii, 1203-1216
- 13 GRAVEY, C J, and PARKINSON, J Digitalis in heart failure with normal rhythm, *Brit Heart Jr*, 1939, i, 27-44
- 14 GOLD, H, and DEGRAFF, A C Studies on digitalis in ambulatory cardiac patients, newer principles of digitalis dosage, *Jr Am Med Assoc*, 1930, xcvi, 1237-1243
- 15 WINSTEIN, W, PLAUT, J, and KATZ, L N Limitations of use of digitalis for ambulatory patients with auricular fibrillation, *Am Jr Med Sci*, 1940, cxci, 498-505
- 16 HARRISON, T R Failure of the circulation, 1939, 2nd edition, Williams and Wilkins Company, Baltimore
- 17 FISHBERG, A M Heart failure, 1937, Lea and Febiger, Philadelphia
- 18 WHITE, P D Heart disease, 1937, 2nd edition, Macmillan Company, New York

- 19 LUTEN, D The clinical use of digitalis, 1936, Charles C Thomas Company, Springfield, Illinois
- 20 LYONS, R H, KENNEDY, A J, and BURWELL, C S The measurement of venous pressure by the direct method, *Am Heart Jr*, 1938, xvi, 675-693
- 21 OPPENHEIMER, B S, and HITZIG, W M Use of circulatory measures in evaluating pulmonary and cardiac factors in chronic lung disorders, *Am Heart Jr*, 1936, xii, 257-271
- 22 NEW YORK HEART ASSOCIATION Nomenclature and criteria for diagnosis of diseases of the heart, 1939, 4th edition, New York Heart Assoc, New York
- 23 PETERS, H C, and VISSCHER, M B Energy metabolism of heart in failure and influence of drugs upon it, *Am Heart Jr*, 1936, xi, 273-291
- 24 KATZ, L N, MENDLOWITZ, M, and KAPLAN, H A Action of digitalis on isolated heart, *Am Heart Jr*, 1938, xvi, 149-158
- 25 STEWART, H J, DITTRICK, J E, CRANG, N F, and WHELLER, C H Action of digitalis in uncomplicated heart disease, *Arch Int Med*, 1938, lxii, 569-592
- 26 GOLD, H, and CATTELL, McK Mechanism of digitalis action in abolishing heart failure, *Arch Int Med*, 1940, lvi, 263-278

GAUCHER'S DISEASE *

I. A CASE WITH HEMOLYTIC ANEMIA AND MARKED THROMBOPENIA; IMPROVEMENT AFTER REMOVAL OF SPLEEN WEIGHING 6822 GRAMS

By HARRY MANDELBAUM, M D , F A C P , LOUIS BERGER, M D , F A C S ,
and MAX LEDERER, M D , *Brooklyn, New York*

II LIPID ANALYSIS OF THE GAUCHER'S SPLEEN

By ALBERT EDWARD SOBEL, B S , CH E , A M , PH D , and IRVING ALLAN
KAYE, B A , M Sc , *Brooklyn*

PART I A CASE WITH HEMOLYTIC ANEMIA AND MARKED THROMBOPENIA

THE subject of Gaucher's disease continues to occupy a fairly prominent position in the medical literature of recent years. The disease is not rare, although the total number of cases reported is not large. The following case is of special interest, first, because it is another instance of Gaucher's disease recognized in the fifth decade, second, because of the presence of an active hemolytic anemia necessitating recourse to splenectomy. The spleen removed is the second largest ever to be reported, and probably the largest specimen that ever taxed the skill of a surgeon.

CASE REPORT

First Admission J H, 39 years of age, first entered the Jewish Hospital on April 13, 1936. His family history was entirely negative. His past history revealed that he had had typhoid fever in 1921, he had been told then that his spleen was enlarged. In 1927, he was operated on for acute appendicitis, the surgeon then noted that the spleen reached almost to the umbilicus. Since 1932, he had suffered from recurrent attacks of weakness due to anemia, with apparent improvement following the use of iron and liver preparations. In 1934, he developed ragweed hay fever, attacks had recurred annually since then. In 1934 an ulcer formed on the inner aspect of the left leg at the junction of the lower and middle thirds, it had not healed up to the time of admission.

He entered the hospital because of weakness, pallor and soreness in the left leg. Weakness and fatigability had been manifest for a few weeks, and of late, shortness of breath had attended moderate physical effort. He had noted an increasing pallor and thought he was somewhat jaundiced. He was positive in the assertion that the girth of his abdomen had steadily increased during the preceding two years.

On admission, the temperature was 100.2° F and the pulse rate was 86 per minute. The blood pressure was 128 systolic and 66 diastolic. The patient's ap-

* Received for publication September 5, 1940
From The Jewish Hospital of Brooklyn, N Y

pearance was striking, the skull was oxycephalic (tower-skull), the torso was barrel-shaped with its greatest diameter at the level of the sixth to the ninth ribs, and the arms, legs and face appeared thin and atrophied. The sclerae were not icteric. Irregular wedge-shaped pingueculae were present. The skin was pigmented by a patchy bronzing more marked on the exposed surfaces. The anterior aspect of each leg was likewise deeply pigmented, and on the left leg an irregular deep ulcer, 5 cm in diameter, was noted 15 cm above the ankle. The spleen, smooth and hard, extended on the right to the midclavicular line and below to an inch above the pelvic brim, the liver was not palpable.

Laboratory Data Blood study erythrocytes, 2,800,000 per cu mm, hemoglobin, 49 per cent (Dare), leukocytes, 8,200 per cu mm, polymorphonuclear neutrophils, 45 per cent, small lymphocytes, 53 per cent, monocytes, 2 per cent, moderate anisocytosis and poikilocytosis. An occasional microcyte was noted which appeared spherical in wet preparations. Reticulocytes, 3 per cent, coagulation time, 5 minutes, bleeding time, 2½ minutes. The fragility test showed

	Patient			Control	
	Washed	Unwashed	Cells	Washed	Unwashed
Hemolysis begins	0.44	0.46		0.44	0.44
Hemolysis complete	0.32	0.32		0.33	0.34

Chemical examination of the blood sugar, 109 mg per cent, urea nitrogen, 21.8 mg per cent, creatinine, 1.3 mg per cent. The cholesterol was low (102 mg per cent). The icterus index was 9, the Van den Bergh, direct, delayed positive, indirect, 175 units. The urine contained no bile, urobilinogen was present in normal amounts.

He received a high caloric-high vitamin diet, liver parenterally and iron by mouth. A diagnosis of hemolytic anemia was made, the etiology was not established. Congenital hemolytic jaundice and Gaucher's disease were considered as possible causes. He left the hospital feeling stronger. The soreness of his left leg had abated but the ulcer had not improved. Parenteral liver injections were continued once weekly for four months, the hemoglobin was raised to 84 per cent and the red blood cell count to 4,100,000 per cu mm.

In October 1938, in spite of careful adherence to diet and medication (liver and iron), he again complained of increasing weakness, pallor and shortness of breath. The spleen filled most of his abdomen, extending to just beyond the mid-clavicular line on the right and dipping into the brim of the pelvis below. The liver was not palpable. He was seen in consultation with Dr Nathan Rosenthal on October 26, 1938, the hemoglobin was 51 per cent (Dare), the erythrocytes, 4,400,000 per cu mm. The leukocytes were 24,200, the platelets, 70,000, polymorphonuclear neutrophils, 53 per cent, eosinophiles, 1 per cent, lymphocytes, 41 per cent, monocytes, 5 per cent, reticulocytes, 5 per cent. An occasional microspherocyte was seen. The icterus index was 10. Bone marrow smears taken from the sternum on two occasions failed to show Gaucher cells, there was a marked preponderance of normoblastic elements, the myelograms were characteristic of hemolytic anemia.

Second Admission The patient reentered the hospital November 17, 1938, a year and a half after his first admission. His complaints were essentially the same, the ulcer on his left leg had not healed. He appeared weaker and more emaciated. The pigmentation was deeper, a slight icteric tint was noted in the sclerae and the pingueculae were more prominent. The anemia was marked. A loud systolic murmur was heard over the mitral and pulmonic areas. The lungs were clear. The spleen occupied most of the abdomen. The liver could not be felt. The pigmentation of both legs was deeper and extended to just below the knees. The ulcer on the left leg measured 3 cm in diameter and ½ cm in depth.

Laboratory Data Blood study erythrocytes, 2,600,000 per cu mm, hemoglobin 40 per cent (Dare), leukocytes, 11,000, polymorphonuclear neutrophils, 46 per cent, band forms, 5 per cent, lymphocytes, 37 per cent, monocytes, 1 per cent. A few microspherocytes were again seen. The blood platelets were 20,000 per cu mm. The fragility test showed

	Washed	Patient Unwashed	Cells	Washed	Control Unwashed
Hemolysis begins	0 44	0 42		0 44	0 44
Hemolysis complete	0 28	0 30		0 30	0 28

Sternal puncture was done by Dr M Morrison, the myelograms failed to show any Gaucher cells, there was evidence of marked leukogenic and erythrogenic activity.

The Kline test with blood was negative. Chemical examination of the blood showed 89 mg per cent of sugar and 17.3 mg per cent of urea nitrogen. The icterus index was 17. The blood cholesterol was unusually low, 87 mg per cent, of which 28 per cent was estimated as free cholesterol. The blood phosphorus was 3 mg per cent and the phosphatase, 3 units per 100 cc. The prothrombin time (Howell's method), was 10 minutes, compared to 6 minutes for the control. Renal tests showed normal function, the urine contained no bile, and urobilinogen was present in normal amounts in the urine.

An adrenalin test was done to test the contractability of the spleen. The result is recorded in table I.

TABLE I

Time	Hgb (Dare)	Erythrocytes Millions per cu mm	Leukocytes per cu mm	PMN %	Bands %	PME %	Lymph %	Mono %
2 00	45%	2 7	11,250	64	7	2	25	2
2 10		Adrenalin chloride, 1			1000, m	VII, injected subcutaneously		
2 25	50%	2 75	12,750	52	4	0	40	4
2 40	50%	2 75	20,900	33	0	0	65	2
2 55	50%	3 25	16,500	38	4	0	56	2
3 10	47%	3 05	13,600	48	4	2	42	4
3 40	47%	3 25	13,850	66	4	0	30	0
4 10	52%	2 83	12,900	62	0	2	34	2

The maximum contraction of the spleen occurred at 2 35 (25 minutes after the injection of adrenalin). The transverse diameter of the spleen, measured at its widest portion, was reduced $8\frac{1}{2}$ cm.

Roentgenograms of the heart and lungs showed nothing remarkable. The bones were carefully studied, the lower dorsal and lumbar vertebrae were normal. The humeri were negative except for slight broadening of the lower end of the shaft. No deformity of the cortex or medulla could be demonstrated. The long bones of the lower extremity were normal except for a slight increased density of the condyles of the femora and of the tibial tuberosities. A slight broadening of the lower ends of the shafts of both femurs was noted.

Impression The degree of anemia had increased progressively during the four weeks preceding his admission, it was associated with a leukocytosis and an increased icterus index, the myelograms showed active erythropoiesis. These facts constituted evidence of an active hemolytic anemia. Was it on a basis of congenital hemolytic jaundice? The family history was negative, microspherocytes were only occasionally found and the fragility of the red blood cells was not appreciably altered. The "tower skull," the presence of a chronic ulcer on his leg and an acholuric icterus in a swarthy individual favored this concept. Gaucher's disease seemed, however, more probable,

the mottled bronze pigmentation with symmetrical brownish-black discoloration of the anterior aspect of both legs, the tremendous spleen and the thrombopenia were suggestive. However, repeated myelograms failed to show any Gaucher cells, and the roentgen-ray studies were not conclusive.

In the presence of an increasing hemolytic anemia and a marked depression of the platelets, it was agreed that splenectomy was indicated.

Splenectomy was done on November 11, 1938, by Dr. Louis Berger. Anesthesia (closed ether primarily, oxygen as indicated). Incision: a left rectus incision extending from the costal arch close to the xiphoid to within 3 inches of the inguinal ligament, about 20 inches long. The spleen occupied most of the abdomen, it extended to the right midclavicular line, reached high under the diaphragm, and below it dipped beneath the pelvic brim. Numerous adhesions were encountered. The splenic pedicle was short, the vessels were very large, each the width of a finger. The gallbladder was distended, no stones could be palpated. The liver appeared slightly enlarged but not abnormal in appearance. Considerable bleeding attended the removal of the spleen, leading to shock, which was successfully combated with a continuous venoclysis of glucose and saline solutions and a transfusion of 1000 cc of citiated blood.

Postoperative Course The patient reacted well, the pulse and blood pressure were normal within 24 hours. Convalescence was uneventful and he was discharged from the hospital on December 7, 1938. Changes in the hemograms before and after splenectomy are recorded in table 2. A sternal puncture was done on December 4, 1938. Dr. Morrison again failed to find any Gaucher cells.

Chemical Studies of the Blood On November 23, the icterus index was 16.1, the Van den Bergh direct, delayed, indirect, 1.26 units per 100 cc blood serum. On November 30, the icterus index was 3.4, the Van den Bergh direct, negative, the indirect, 0.35 units per 100 cc blood serum. Cholesterol On November 23, total, 89 mg per cent, 23 per cent as free, cholesterol on November 30, total, 146 mg per cent, 40 per cent as free. On November 30, the blood calcium was 9.8 mg per cent, the phosphorus was 5.2 mg per cent and the phosphatase was 6.8 units per 100 cc.

Pathological Report (Dr. Max Lederer) *Gross* The spleen measured 38 by 24 by 13 cm and weighed 6822 grams. The external surface was nodular, smooth and glistening and conformed to the original shape of a spleen. Scattered throughout were numerous firm nodules which on section appeared as irregular gray areas, up to 2 cm in diameter and well demarcated from the surrounding tissue. The spleen was divided into lobules of different size by thin and broad gray streaks, some of these lobules projected slightly above the cut surface. Throughout there was a honey-combed appearance of the parenchyma, and spaces up to 0.3 cm were filled with blood. The blood vessels were prominent and distended with blood. The Malpighian corpuscles could not be recognized.

Microscopic The usual cytoarchitecture of the spleen was obscured and not readily discernible. The capsule and the trabeculae were definitely thickened. The Malpighian bodies were not evident excepting in occasional areas where they appeared as small oval masses. Throughout the preparation, the sinuses were markedly distended, many were so distended as to give an angiomatous picture, the sinuses were lined with endothelial cells. Within the distended sinuses were large cells containing one or more vesicular nuclei and abundant cytoplasm in which linear streaks could be seen. In other cells, the nuclei were placed near the periphery or were absent. These Gaucher cells varied greatly in size, and in different areas in their number as well. Small hemorrhagic foci were noted. In some areas there were foci of dense hyalinized fibrous connective tissue with scattered purple blue staining deposits (calcium). Scattered throughout the preparation were accumulations of mononuclear cells containing golden-brown granules in their cytoplasm. With the

Perl stain, iron pigment was seen lying free in the tissue as well as within these large mononuclear cells, occasionally, iron pigment in small amounts was noted within a Gaucher cell. With the Laidlaw connective tissue stain, a fine reticulation was seen traversing the preparation, forming dense masses in the trabeculae. Microchemical stains suggested the lipid in the cells to belong to the kersin type rather than the phosphatid. Diagnosis Splenomegaly, lipid histiocytosis of the Gaucher type.

Lipid Analysis of the Spleen See supplement

Subsequent Course He continued to improve. Three months after his operation, he returned to work for the first time in five years. The ulcer on his leg healed shortly after he left the hospital and has not recurred. At the end of six months, he weighed 208 pounds (he weighed 153 pounds when he had been discharged from the hospital), his general appearance had changed, his skin was fair, his face and extremities were well rounded, and the lower thoracic bulge was not as conspicuous. On May 25, 1940, he weighed 227 pounds, his skin was fair but the pigmentation of the legs was still evident. The blood count was normal (table 2). Roentgenograms of all the bones show no changes from those previously taken. The pinguiculae had completely disappeared. He was married in June 1940.

TABLE II

Date	Hgb (Dare) %	Erythrocytes Millions per cu mm	Leukocytes per cu mm	PMN %	Bands %	PME %	PMB %	Lymph %	Mono %	Platelets per cu mm
11-17	40	2.65	11,100	47	5	0	2	37	9	20,000
11-18	47	2.78	11,500	51	3	0	0	39	7	20,000
11-21	45	2.7	11,250	52	5	0	0	41	2	55,000
11-22	Splenectomy Transfusion 100 c c citrated blood									
11-23	45	2.92	28,000	74	9	0	0	17	0	
11-25	59	2.95	20,000	83	0	0	0	8	9	
11-26	45	2.82	19,000	64	2	2	0	24	8	
11-28	45	2.54								
11-30	42	3.2								760,000
12-2	47	2.85								
12-6	53	2.73								
12-15	64	3.8	11,000	65	3	0	0	25	7	
12-29	82	4.3	7,400	64	2	0	0	28	6	340,000
1-15	88	4.4	7,100	67	3	0	0	29	1	310,000
2-15	91	4.7	6,400	65	2	0	0	28	5	
3-18	98	5.1	6,200	58	0	0	0	37	5	
5-14	97	5.1	6,100	62	2	0	0	32	4	240,000
6-16	97	5.2	6,900	68	3	1	1	23	4	210,000
5-25	98	5.3	5,400	61	3	2	1	29	4	

Preoperative and postoperative blood studies. Patient received a transfusion immediately following splenectomy. He had received no hematinics. Note the thrombopenia before operation.

DISCUSSION

Gaucher⁷ first described the disease in 1882 as a primary epithelioma of the spleen. Mandelbaum and Downey¹³ in 1916 established this condition as a metabolic disturbance. In 1924, Lieb¹² and Epstein,⁵ by chemical analyses of Gaucher spleens, showed that kersin, a cerebroside, was the most important lipid constituent.

Gaucher's disease is regarded as a non-hereditary, congenital familial disease linked with a constitutional factor involving a disturbance in lipid metabolism, one of the primary xanthomatoses.

A classical description of the disease was presented by Mandelbaum and Downey in 1916 "Gaucher's disease begins usually in childhood or infancy, often affects several members of a family of the same generation and is characterized by progressive increase in the size of the spleen which frequently enlarges to an enormous size, and by subsequent enlargement of the liver. A characteristic discoloration (brownish-yellow) of the skin is present, usually confined to the exposed parts of the body (the face, neck and hands) and a peculiar yellowish, wedge-shaped thickening of the conjunctivae of both sides of the cornea, is seen" (pingueculae)

Some doubt has been cast on the non-hereditary character of the disease by Anderson¹ who studied a family in which there was the possibility of transmission through an unaffected male to four of his daughters

Gaucher's disease shows a predilection for those of the Jewish race. It occurs in females twice as often as in males. The condition is usually discovered in childhood, Horsley et al.⁹ reviewed 71 cases from the literature and noted that 56 per cent of the cases had been recognized before the age of eight. Wechsler and Gustafson's patient¹⁷ was 68 years old.

The onset is insidious. In some, constant abdominal discomfort may cause them to seek medical advice at which time a large spleen is discovered. Involvement of the bones may be heralded by pain, occasionally severe enough to resemble osteomyelitis (Capper et al.³). Pick¹⁵ has described a type predominantly osseous, he reported two such cases in brothers. On roentgen-ray studies, the bones appear less opaque because of a deficiency in calcium. Occasionally, the shafts of the long bones present a picture of an apparently reduplicated cortex. Welt et al.¹⁸ found the earliest change to be a fusiform expansion of the lower one-third of the femur (the Erlenmeyer-flask-like femur).

The splenic enlargement is the important feature of Gaucher's disease. In Pick's¹⁵ cases, the average size for children between the ages of 5 to 14 was 1800 gm, the average size for adults was 2700 gm, normally the weight of the spleen ranges from 150 to 160 gm.¹¹ Pick¹⁵ refers to the largest spleen he had observed as weighing 8100 gm. In the case reported by Horsley et al.,⁹ the spleen weighed 5890 gm.

A diffuse or spotty pigmentation especially marked on the exposed parts is of frequent occurrence. Bloom et al.² emphasized the presence of symmetrical areas of pigmentation involving the anterior aspect of the legs in a number of their cases, occasionally an ulcer formed. The pigmentation is an expression of a general hemochromatosis which is constantly present in this disease. The bilateral conjunctival pingueculae are likewise evidence of the hemochromatosis, it was noted in 14 of the 89 cases reviewed by Hoffman and Makler.⁸

The blood changes, according to Pick,¹⁵ consist first of a leukopenia which may be due to a decrease in the polymorphonuclear neutrophils or the lymphocytes, then there follows a moderate hypochromic anemia.

Thrombocytopenia is a constant feature and may be observed early. Marked evidence of myelophthysis may eventuate due to crowding of the bone marrow by Gaucher cells. Gaucher cells have never been observed in the peripheral blood but their recognition in the bone marrow smear is almost a constant finding. Hemolysis is of common occurrence, it is a factor in the production of the anemia and is the source of hemosiderin that is widely deposited (hemochromatosis). The blood platelets may be strikingly diminished and in the terminal phases of the disease, purpuric manifestations are not unusual. However, it is speculative to assume a direct relationship between the thrombocytopenia and these hemorrhagic tendencies (Eagle⁴).

The origin of the Gaucher cell is not definitely known. Mandelbaum and Downey¹³ and Kettle¹⁰ stated their conviction that it probably arises from the reticulum cell. Erf⁶ studied fresh Gaucher cells as seen in supravital preparations and found that morphologically they are similar to reticulum cells. Pick¹⁵ took exception to the inclusion of Gaucher's disease as a reticuloendothelial disease or a histiocytomatosis, because, "in addition to the reticulum cells of the liver and spleen, the parent cell includes also the connective tissue cells of the blood vessels of the adventitia and periadventitia and, in addition, the cells of Glisson's capsule."

Pathology The primary pathologic feature is the Gaucher cell. "They have a distinctive appearance¹³, they are fibrillated and show a characteristic longitudinal streaking. They are often elongated and fused into long strands. The nucleus, multiple as a rule, is often irregular in outline, eccentric in position and wrinkled in appearance." As many as 21 have been encountered in one cell¹⁵. The cells measure from 20 to 80 μ in their largest diameter. The large cell infiltration is usually limited to the spleen, liver, lymph nodes and bone marrow, an instance of renal invasion was reported by Horsley et al.⁹ In the spleen, the venous sinuses are lined by Gaucher cells, obliterating the Malpighian corpuscles and crowding the normal pulp cells into enveloping bands. Similarly, the parenchyma of the liver may be "crowded out," the liver lobules disintegrated and a peculiar cirrhotic thickening of Glisson's capsule may occur¹⁵. Hemosiderin is deposited widely, it is found in the cells of the splenic trabeculae, in the endothelial cells of the venous sinuses (histiocytes) and in the Gaucher cells as well.

Treatment Potter and McRae¹⁰ report apparent improvement and decrease in the size of the spleen following the continued oral administration of liver extract. Pick¹⁵ would limit splenectomy only to those cases in which anemia is prominent, a hemorrhagic diathesis is manifest or a tremendous spleen is producing mechanical obstructive symptoms. He noted involvement of the osseous system, beginning and progressing rapidly after splenectomy. This also occurred in the case reported by Melamed and Chester¹⁴. There has been no enthusiasm for the results following irradiation of the spleen.

Case Discussion The problem presented for diagnosis was one of

hemolytic anemia complicating a tremendous splenomegaly. The patient presented a typical tower skull, hemolytic activity was evidenced by an increasing anemia, a leukocytosis, increased erythrogenic activity of the bone marrow and an increased icterus index, an occasional microcyte that appeared spherical on wet preparations, was seen, all favored a diagnosis of congenital hemolytic jaundice. On the other hand, the tremendous size of the spleen, the general pigmentation of the skin, the symmetrical pigmentation of his legs and the prominent pinguiculae seemed conclusive of Gaucher's disease. A marked thrombocytopenia was considered as an added characteristic. The roentgen-ray studies of the bones were not conclusive. Repeated myelograms failed to reveal a single Gaucher cell after careful search. It was remarkable that with a depression of the platelets to 20,000 per cubic millimeter there were no purpuric manifestations. Liver extract, for a number of years, had apparently been able to maintain a fair hemic state. However, in the several months preceding his second admission to the hospital, it proved unable to interrupt the progress of an increasing hemolytic anemia. It was agreed that splenectomy was indicated. Following the removal of the spleen the hemoglobin and red blood cell values progressively improved, to reach normal in five months and have continued so since. Excepting for the areas on his legs, pigmentation is no longer evident, his skin is fair and the pinguiculae have disappeared. Subsequent roentgen-ray studies of the bones (19 months after splenectomy) show no evidence of bone lesions. The liver has not enlarged. An ulcer of his leg, of years' duration, promptly healed, and has not recurred. Unusually low blood cholesterol values were obtained before operation.

SUMMARY

A case of Gaucher's disease in a man of 41 has been presented. Liver extract which had apparently been helpful in maintaining a fair hemic level, ultimately became ineffective. An active hemolytic anemia was the indication for splenectomy, by means of which a remission was induced. The spleen weighed 6822 grams. The patient has shown remarkable continued improvement since the operation, including the disappearance of the pinguiculae and the general pigmentation.

REFERENCES

PART I

- 1 ANDERSON, J. P. Hereditary Gaucher's disease, *Jr Am Med Assoc*, 1933, *ci*, 979-981.
- 2 BLOOM, T. F., GROEN, J., and POSTMA, C. Gaucher's disease, *Quart Jr Med*, 1936, *v*, 517-527.
- 3 CAPPER, A., EPSTEIN, H., and SCHLESS, R. A. Gaucher's disease. Report of a case with presentation of a table differentiating the lipid disturbances, *Am Jr Med Sci*, 1934, *clxxxviii*, 84-92.
- 4 EAGLE, H. Recent advances in the blood coagulation problem, *Medicine*, 1937, *xxvi*, 95-138.

- 5 EPSTEIN, EMIL Beitrag zur Chemie der Gauchereschen Krankheit, *Biochem Ztschr*, 1924, cxlv, 398-414
- 6 ERF, L A Studies of Gaucher cells by the supravital technique, *Am Jr Med Sci*, 1938, cxcv, 144-150
- 7 GAUCHER, PHILIPPE-CHARLES-ERNEST De l'epithelioma primitif de la rate hypertrophie idiopathique de la rate sans leucemie, Thèse de Paris, 1882, iii, 3-31
- 8 HOFFMAN, S J, and MAKLER, M L Gaucher's disease. A review of the literature and report of a case diagnosed from section of an inguinal lymph gland, *Am Jr Dis Child*, 1929, xxxviii, 775-793
- 9 HORSLEY, J S, BAKER, J F, and APPERLY, F L Gaucher's disease of late onset with kidney involvement and huge spleen, *Am Jr Med Sci*, 1935, cxc, 511-518
- 10 KETTLE, E H The splenic lesions in some cases of splenomegaly associated with secondary anemias, *Jr Path and Bact*, 1919-1920, xxiii, 413-424
- 11 KRUMBHAR, E B, and LIPPINCOTT, S W The postmortem weight of the "normal" human spleen at different ages, *Am Jr Med Sci*, 1939, cxcvii, 344-358
- 12 LIEB, H Cerebrosidspeicherung bei Splenomegalie, Typus Gaucher, *Ztschr f physiol Chem*, 1924, cxl, 305-313
- 13 MANDELBAUM, F S, and DOWNEY, H S The histo-pathologic biology of Gaucher's disease (large cell splenomegaly), *Folia haemat*, 1916, xx, 139-202
- 14 MELAMED, S, and CHESTER, W Osseous form of Gaucher's disease, *Arch Int Med*, 1938, lxi, 798-807
- 15 PICK, LUDWIG A classification of the diseases of lipid metabolism and Gaucher's disease, *Am Jr Med Sci*, 1933, clxxxv, 453-469
- 16 POTTER, E B, and McRAE, C C Gaucher's disease report of 2 cases with a remission in 1 following administration of liver extract, *Am Jr Med Sci*, 1933, clxxxv, 92-96
- 17 WECHSLER, H F, and GUSTAFSON, E Gaucher's disease, associated with multiple telangiectases in elderly woman, *N Y State Med Jr*, 1940, xl, 133-135
- 18 WELT, S, ROSENTHAL, N, and OPPENHEIMER, B S Gaucher splenomegaly with special reference to skeletal changes, *Jr Am Med Assoc*, 1929, xcii, 637-644

PART II LIPID ANALYSIS

Recently our attention was called by Dr Harry Mandelbaum to the fact that a spleen would be removed from a patient suspected to be suffering from Gaucher's disease. This gave us an opportunity to survey the literature and select a method for the lipid analysis of the spleen before its actual removal from the patient. Analyses on freshly removed Gaucher's spleens are rare, most have been performed on formaldehyde-fixed specimens. It has been shown that specimens so preserved undergo changes in their lipid composition^{6, 7}

The method selected for the analysis was based upon that of Sobotka, Glick, Reiner and Tuchman¹³. Our procedure differed in that we extracted all the lipids first and fractionated them subsequently, whereas Sobotka and his associates fractionated by extracting with preferential solvents.

The general scheme of analysis involved a preliminary extraction of the fresh spleen with hot alcohol followed by ether. The combined extracts were purified by re-resolution in hot absolute alcohol and absolute ether in order to eliminate inorganic material. Cerebrosides and phospholipids were

separated from sterols and neutral fat by the addition of acetone to the residue left after evaporating the absolute alcohol and ether, the cerebrosides and phospholipids being insoluble in this solvent. These two fractions were then analyzed for nitrogen, phosphorus and free and total cholesterol.

In the calculations, the phosphorus values were assumed to be derived from lecithin. Esterified cholesterol was assumed to be cholesterol oleate. The difference between the weights of the acetone-soluble residue and the combined weights of phospholipids, cholesterol and cholesterol esters was assumed to be neutral fat and free fatty acids. The difference between the weights of the acetone-insoluble fraction and the phospholipids was expressed as the cerebroside fraction. The method of isolating the kerafin from the spleen and its properties was described in a separate paper⁸. Pure kerafin was isolated from a large weight of spleen and its identity proved by the selenite plate test¹² and the formation of the methyl ester of lignoceric acid on acid hydrolysis in methyl alcohol.

PROCEDURE

Fifty grams of finely hashed spleen, which had been preserved in a well-stoppered bottle by the addition of a few drops of chloroform, were suspended in 100 ml of boiling 95 per cent alcohol. The suspension was refluxed one hour and then filtered while hot into a weighed beaker. The alcoholic filtrate was evaporated to dryness at 60° C according to Kirk et al.¹⁰ This procedure was repeated nine times more, making 10 extractions in all. The residue was then further extracted an equal number of times with 100 ml portions of ethyl ether. The ethereal filtrates were collected in the same weighed beaker which was reweighed after evaporating the ether to dryness. The lipid-free splenic residue was dried at 100° C for a few hours and weighed. This weight and the weight of the material in the weighed beaker represent the dry weight of the spleen.

To purify the lipids extracted, the residue in the beaker was reextracted with boiling absolute alcohol and filtered. The filtrate was collected in a weighed beaker. The residue was washed several times with boiling absolute alcohol and finally with absolute ether. The combined filtrates were then evaporated to dryness at 60° C. The weight of this extracted material was taken to represent the lipid content of the sample.

The lipids were fractionated by extraction with boiling acetone. The material insoluble in boiling acetone was washed several times with successive portions of boiling acetone and then dried in a vacuum desiccator and weighed. The acetone filtrate was allowed to cool down to room temperature and the slight precipitate which formed was separated by filtration and added to the acetone-insoluble fraction. It was then washed thoroughly with cold acetone, dried at 60° C and weighed. The acetone washings, collected in a weighed beaker, were evaporated to dryness and the beaker reweighed.

Weighed amounts of each fraction were dissolved in benzene and made up to a definite volume. Aliquots were then taken for the following analyses

- 1 Phosphorus, determined by the method of Fiske and Subbarow ⁴
- 2 Free and total cholesterol, determined by the method of Kaye ⁹
- 3 Nitrogen, determined by the method of Stover and Sandin ¹⁵

The results are presented in tables 1, 2, and 3

TABLE I
Major Fractions of Gaucher's Spleen

Per Cent Solids	Per Cent Lipid in Solids	% Distribution of Lipids		
		Soluble in Cold Acetone	Insoluble in Cold Acetone	Soluble in Hot, Insoluble in Cold Acetone
25.1	17.6	29.1	68.9	2.0

TABLE II
Per Cent Composition of Lipid Fractions

Fraction	Free Cholesterol	Esterified Cholesterol	Phosphatides	Balance (Neutral fat + acids)	Balance (Cerebrosides)
Soluble in acetone	25.6	6.7	12.2	55.5	
Insoluble in acetone	0	0	46.7		53.3

TABLE III
Lipid Fractions in Fresh Gaucher's Spleens Per Cent Composition of Total Lipids

	Free Cholesterol	Esterified Cholesterol	Phosphatides	Neutral Fat and Fatty Acids	Cerebrosides
Present authors	7.6	2.0	36.2	16.5	37.6
Sobotka et al ¹³	11.6	0.5	17.7	33.6	36.6
Three Gaucher spleens	6.5 4.0	7.5 10.2	33.5 21.9	26.4 35.6	26.1 27.9
Average of 3 control spleens, Sobotka et al ¹³	10.7	1.5	41.5	26.9	21.0

The percentage lipid on the dry basis as seen in table 1 is less than that observed by most workers in adults suffering from Gaucher's disease ^{13, 1, 3, 11}. This difference, however, may be due in part to the fact that the spleen lipids were purified in our case from most inorganic substances by re-extraction of the lipid extract with anhydrous alcohol and ether. The nitrogen content of the acetone soluble fraction was 2.43 per cent. This amount is higher than would be required for the phosphatides, thus the pres-

ence of other nitrogen containing substances is indicated. This may possibly be due to some urea, as shown recently by Christensen² and Folch and Van Slyke⁵ for the lipid extracts of blood. In the acetone insoluble fraction, the nitrogen content was 4.63 per cent which is higher than the amount required for the phosphatides and cerebrosides. Here again it is possible that some urea was present. Thus both the cerebroside and the neutral fat and fatty acid fractions are over stated by the amount of nitrogenous contaminants present.

The acetone extraction as seen in table 2 effected a cleancut separation of cholesterol and its esters but not of the phosphatides. The solubility of neutral fat and fatty acids in acetone is similar to that of cholesterol and its esters, and therefore a complete separation of these constituents by means of this solvent was probably accomplished.

In table 3, the results obtained are compared with the analyses of Sobotka et al.¹³ The neutral fat and fatty acids are lower in our spleen than those obtained by Sobotka et al.¹³ even in their normals, while phosphatides and cerebrosides are higher than those of their Gaucher's spleens. The cerebrosides in our spleen are higher than those obtained in their normals but the phosphatides are slightly lower. The combined cerebrosides and phosphatides are much higher than in their Gaucher's spleens and higher than in their normal spleens. Our findings illustrate even better than do Sobotka's his theory that disturbances in fat metabolism are usually at the expense of the neutral fat portion.¹⁴

SUMMARY

A Gaucher's spleen was analyzed for lipids. The characteristic lipid constituent, kersasin, was isolated and identified. An increase of the cerebrosides at the expense of neutral fat was observed.

REFERENCES

PART II

- 1 BLOOM, W., and KERN, R. Spleens from Gaucher's disease and lipoid-histiocytosis, chemical analysis, *Arch Int Med*, 1927, **xxxix**, 456-461.
- 2 CHRISTENSEN, H. N. Contaminants of blood phospholipids, *Jr Biol Chem*, 1939, **cxxix**, 531-537.
- 3 EPSTEIN, E. Beitrag zur Theorie und Morphologie der Immunität. Histiocytenaktivierung in Leber, Milz und Lymphknoten des Immuntieres (Kaninchen), *Virchow's Arch f path Anat*, 1929, **cclxxiii**, 89-115.
- 4 FISKE, C. H., and SUBBAROW, Y. The colorimetric determination of phosphorus, *Jr Biol Chem*, 1925, **lxvi**, 375-400.
- 5 FOLCH, J., and VAN SLYKE, D. D. Nitrogenous contaminants in petroleum ether extracts of plasma lipids, *Jr Biol Chem*, 1939, **cxxix**, 539-546.
- 6 HALLIDAY, N. Effect of formalin fixation on liver lipids, *Jr Biol Chem*, 1939, **cxxix**, 65-69.

- 7 HALLIDAY, N, DEUEL, H J, JR, TRAGERMAN, L J, and WARD, W E On isolation of glucose-containing cerebroside from spleen in case of Gaucher's disease, *Jr Biol Chem*, 1940, cxxxii, 171-180
- 8 KAYE, I A Rapid method for the isolation of kerašin from a Gaucher spleen, *Jr Lab and Clin Med*, 1940, xxv, 1117-1118
- 9 KAYE, I A Determination of total and free cholesterol in blood serum, *Jr Lab and Clin Med*, 1940, xxv, 996-1001
- 10 KIRK, E, PAGE, I H, and VAN SLYKE, D D Gasometric microdetermination of lipids in plasma, blood cells, and tissues, *Jr Biol Chem*, 1934, cvi, 203-234
- 11 McCONNELL, J S, FORBES, J C, and APPERLY, F L Notes on chemical studies of Gaucher spleen, *Am Jr Med Sci*, 1939, cxcvii, 90-92
- 12 ROSENHEIM, O Galactosides of the brain, *Biochem Jr*, 1913, vii, 604
- 13 SOBOTKA, H, GLICK, D, REINER, M, and TUCHMAN, L R Lipoids of spleen and liver in various types of lipoidosis, *Biochem Jr*, 1933, xxvii, 2031-2034
- 14 SOBOTKA, H The chemistry of the sterids, 1939, Williams and Wilkins Co, Baltimore, pp 82, 83
- 15 STOVER, N M, and SANDIN, R B Use of boric acid in micro-Kjeldahl determination of nitrogen, *Ind and Eng Chem*, 1931, Anal Ed, cxi, 239-240

ELECTROENCEPHALOGRAPHIC CHANGES DURING HYPERVENTILATION IN EPILEPTIC AND NON-EPILEPTIC DISORDERS *

By NORMAN Q BRILL, M D , and HERTA SEIDEMANN, M D ,
New York, N Y

THE clinical observation that attacks of petit mal can be induced by hyperventilation led us to the utilization of this procedure as a routine measure in electroencephalographic examination of patients with known or suspected epilepsy. Since the casual electroencephalographic examination of such patients in the interval between attacks frequently resulted in normal records, it was felt that a higher percentage of positive records could be obtained if the patients were hyperventilated during the examination. This expectation was borne out not only in petit mal epilepsy but also in grand mal, but, because of previously reported changes in the electroencephalogram produced by hyperventilation in normals, it was necessary to compare the changes in epileptics with those obtained in non-epileptics to determine the reliability of the findings as a diagnostic criterion of the presence of an epileptic type of cerebral dysrhythmia. The effect of hyperventilation on the electroencephalogram of 50 patients with known epileptic disorders was, therefore, compared with the effect of this procedure on 50 non-epileptic patients.

METHOD

The epileptic group was composed of patients with idiopathic grand mal epilepsy, petit mal epilepsy, mixed grand and petit mal disorders, and patients with symptomatic epilepsy secondary to organic disease of the brain. The non-epileptic group was a mixed one being composed of some normals and patients suffering from functional and organic diseases of the nervous system.

At the beginning of the investigation, records were taken with a two channel ink-writing electroencephalograph but this was later replaced by a four channel ink-writing electroencephalograph built by Mr. A. M. Grass of the Harvard Medical School. Recordings of the same patient, with the two machines were practically identical.

Simultaneous recordings from the right and left hemispheres with the electrodes placed in the frontal, motor and occipital regions on each side were generally taken on all patients. In some patients, temporal, parietal

* Read at a meeting of the Section of Neurology and Psychiatry of the New York Academy of Medicine, December 10, 1940. Received for publication March 20, 1941.

From the Neurophysiology and Neurological Divisions, Montefiore Hospital, New York. This work was aided by grants from the Frances and John L. Loeb Foundation in memory of Arthur Lehman, and the Hilda Stich Stroock Fellowship Fund.

and vertex leads were also applied when more accurate localization of a pathological focus was desirable. Many of the patients were examined on two or more different occasions.

Before records were taken, the patients received instruction concerning the hyperventilation. They were asked to inhale and exhale as deeply and as rapidly as possible. They were told to disregard a feeling of light-headedness, if it came on, and in most of the patients, the cooperation was excellent.

A record of at least several minutes' duration, and in many of the patients for a much longer time, was taken with the patient in a resting state. At a verbal command, hyperventilation was begun, and it was continued for two to five minutes. In some cases, it was necessary to encourage the patient to continue the hyperventilation for the desired length of time. The record was continued during the period of hyperventilation and always for several minutes after hyperventilation had stopped.

All records showing high amplitude, slow waves varying in frequency from 2 to 4 per second, with or without spikes or notches, occurring in brief bursts or long runs, were considered definitely abnormal, since we found, as have others, that this dysrhythmia occurred not only in petit mal but also, though not as consistently, in grand mal epilepsy in the interval between attacks.

Records showing numerous slow waves of low amplitude (less than 100 microvolts) or isolated brief runs (less than one second) of slow waves whose amplitude was only slightly greater than the alpha activity were considered questionably abnormal.

When artefacts caused by movement or muscle tremor were excluded, pure spike activity was seen to be a very infrequent finding. All records were analyzed for the occurrence of bursts or runs of the high amplitude, slow waves, and comparisons made between the records before and during (or after) hyperventilation.

In this study, we were not concerned with asymmetries between the two sides, or with irregularities in frequency of the alpha activity which were seen in many of the patients with organic brain disease, though these findings were important in the interpretation of individual records.

Records taken before hyperventilation, with the patient quiet, will be referred to as spontaneous records.

RESULTS

Idiopathic Epilepsy Of 22 patients with grand mal epilepsy, only four had definitely abnormal spontaneous records, and 15 had records which were questionably abnormal. During hyperventilation, 18 of the 22 patients, or 82 per cent, had abnormal records with typical outbursts or long runs of high amplitude, slow waves, in many cases with spikes or notching, and four patients had questionably abnormal records (figure 1). In the petit

mal group, two of three patients had abnormal spontaneous records and one a questionably abnormal record. During hyperventilation, all three patients had definitely abnormal records. In the group with both grand and petit mal epilepsy, two of six patients had definitely abnormal spontaneous records. During hyperventilation, five had definitely abnormal records (figure 2). Of 31 patients, therefore, with idiopathic epilepsy, only eight showed abnormal spontaneous records, while 26 or 84 per cent showed abnormal records during hyperventilation.

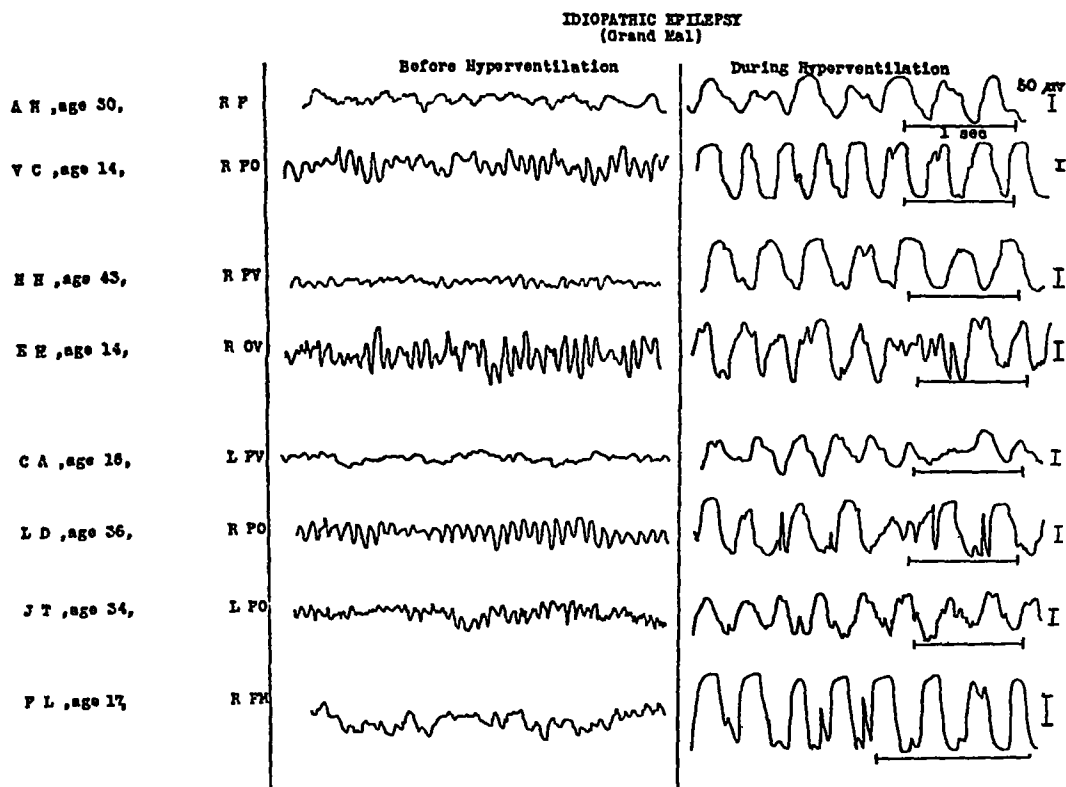


FIG 1 Sections from electroencephalograms of eight patients with idiopathic grand mal epilepsy. A marked dysrhythmia is induced in each case by hyperventilation. In some cases, as in L D, the spontaneous record is normal. The initials at the left of the spontaneous records refer to the areas of the skull from which the recordings were taken. F, M, O, V, representing Frontal, Motor, Occipital and Vertex. R and L refer to right and left. The amplification and time scale varies in the different records. The marker at the extreme right indicates the size of a 50 microvolt signal, and the horizontal line under the record indicates an interval of one second. The same symbols will be used in subsequent figures.

Symptomatic Epilepsy In the group with symptomatic epilepsy, four of 19 patients showed the typical spontaneous outbursts of the high amplitude, slow waves, while during hyperventilation, 10, or 53 per cent, were definitely abnormal (figure 3). In this group, six patients had normal records before and during hyperventilation.

Non-Epileptic Group The non-epileptic group consisted of patients with organic disease of the brain, patients with psychoneuroses and normals.

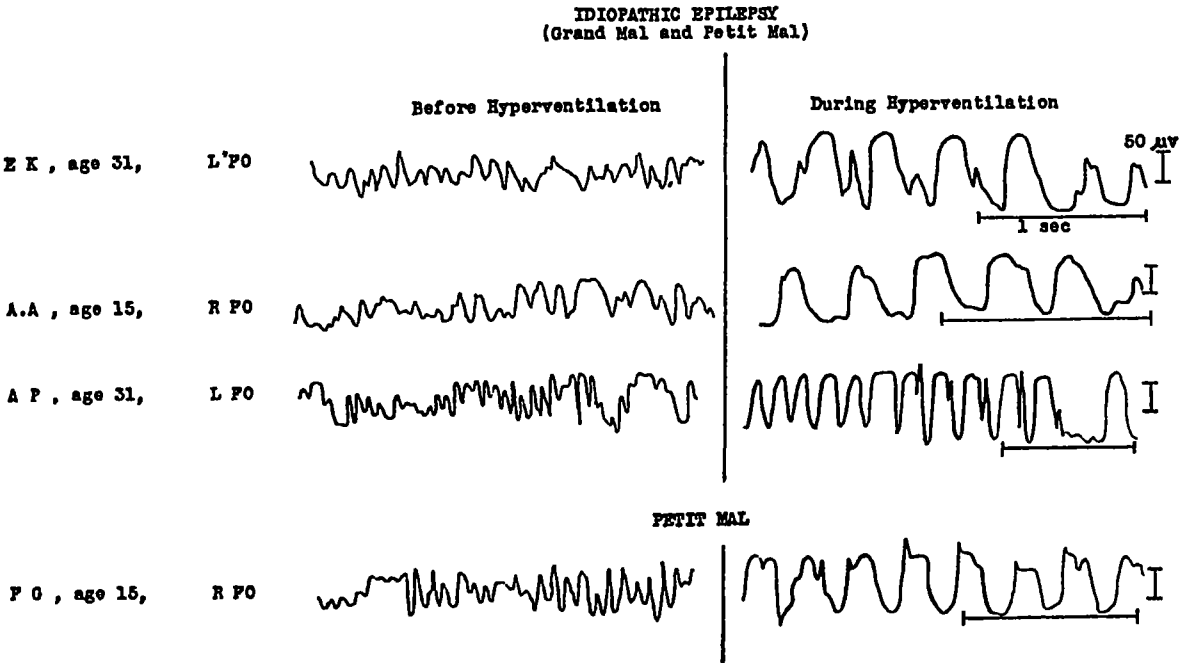


FIG 2

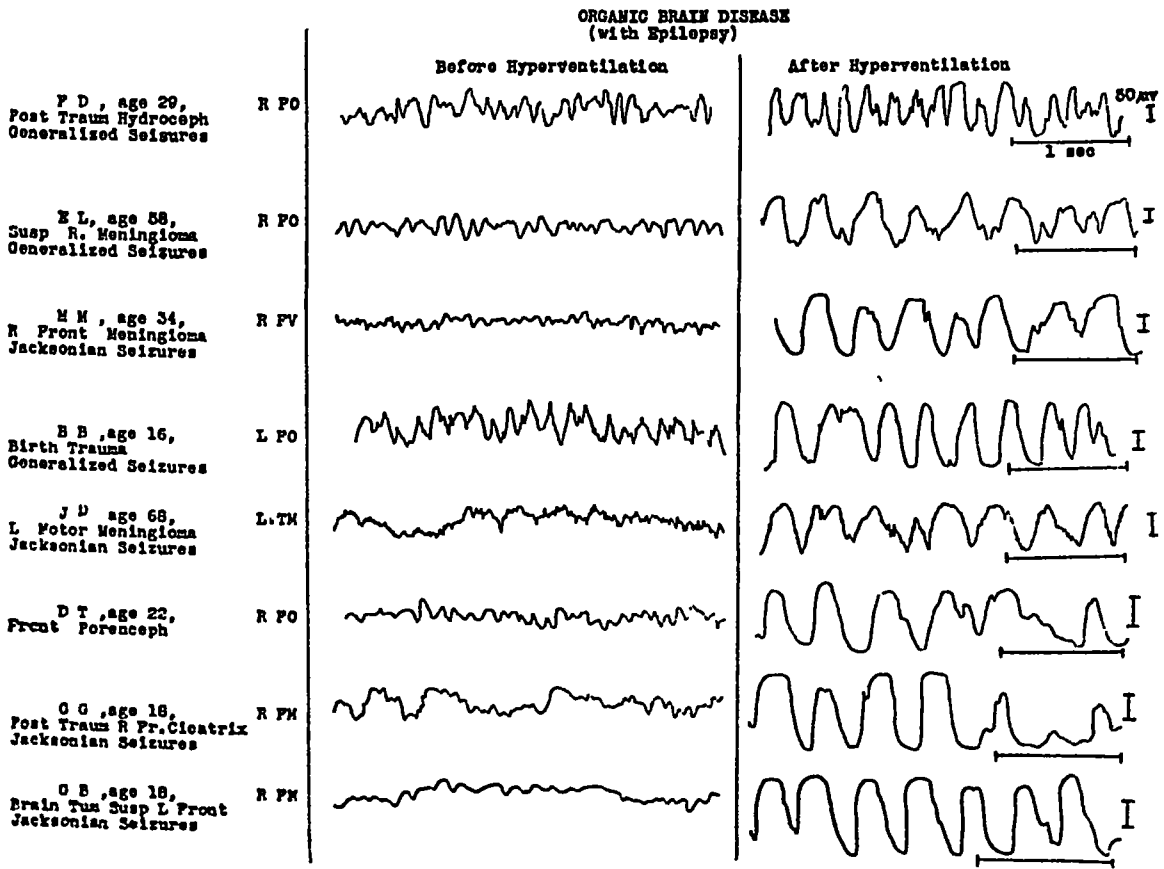


FIG 3.

The group with organic disease of the brain included patients with cerebral arteriosclerosis, brain tumors, Sydenham's chorea, degenerative disease of the nervous system, multiple sclerosis, dystonia musculorum deformans, general paresis, encephalitis, Alzheimer's disease and post-traumatic encephalopathy.

Of 25 patients comprising this group, five showed abnormal spontaneous records. Four of these were patients with chorea and one was a patient with a temporal lobe glioma who had experienced episodes of loss of consciousness without any convulsive phenomena. During hyperventilation, 12, or 48 per cent, showed abnormal records (figure 4). It is of great in-

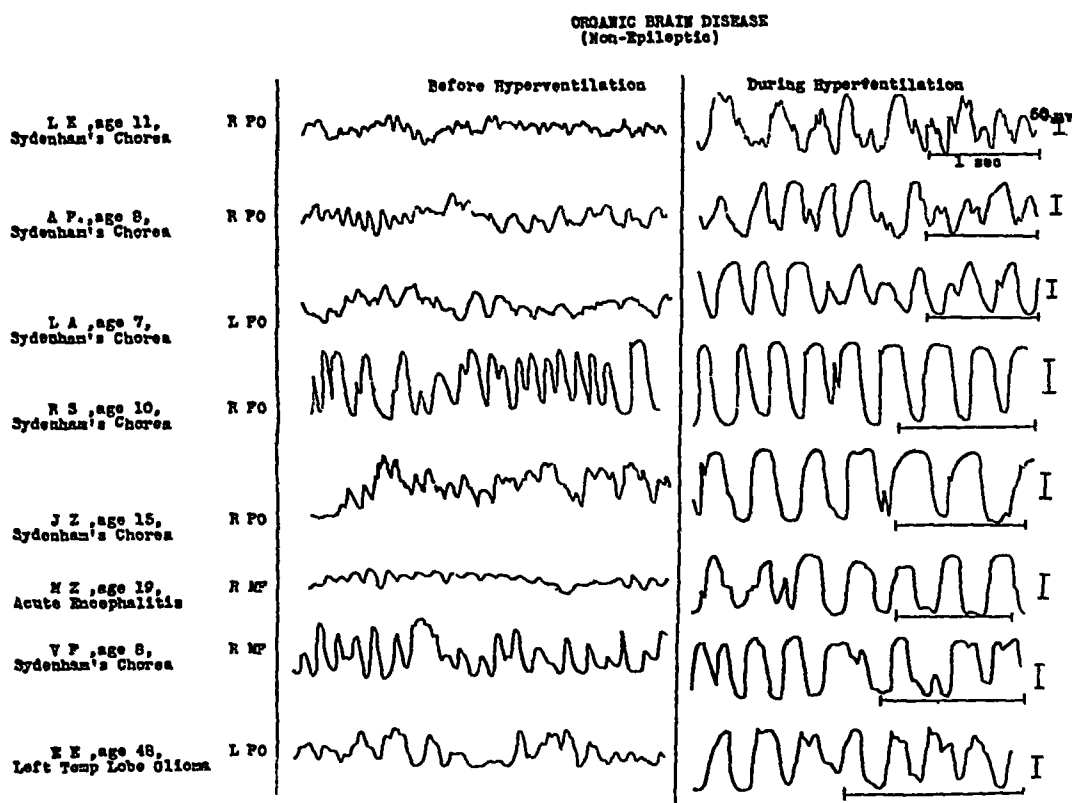


FIG 4

terest to note that of eight patients with Sydenham's chorea, all showed abnormal records during hyperventilation.

There were eight patients in the psychoneurotic group. All of them had normal records before and during hyperventilation.

Records were obtained on nine normals. None had abnormal spontaneous records. Hyperventilation produced no significant change in any of the records.

The miscellaneous group consisted of four patients with migraine, two with severe behavior disorders, one with dizziness of undetermined cause and one with hyperparathyroidism. Of these, none showed an abnormal

It is to be emphasized that from none of the patients, except those with petit mal, who showed this petit mal-like activity could a history of petit mal be elicited, nor was there any apparent or admitted disturbance in consciousness during the examination. Unfortunately, the reaction time of the patients was not tested as was done by Schwab¹⁰ during bursts of the abnormal activity. However, even if the reaction times were found to be increased, it could not be assumed that a specific petit mal disorder existed.

That the abnormal activity was not caused by tetany was proved many times in the course of this study. During hyperventilation in many patients, there were overt signs of tetany without any disturbance in the electroencephalogram. In no case—showing abnormal activity, did tetany appear simultaneously with the abnormality in the record. In some instances, the tetany appeared before and in some after. Many times, the tetany was present long after the record had returned to normal. Nor were the abnormalities a result of disturbances in consciousness or faintness produced by hyperventilation. In no case did these complications supervene. This is similar to the experience of Jung,⁷ who emphasized the fact that the specific epileptic dysrhythmia produced by hyperventilation did not occur in tetany, cardiac attacks or spells of dizziness. Also, it is to be emphasized that there is a marked difference between the slow waves described by Gibbs and his co-workers, as occurring in normals in states of impaired consciousness, and the dysrhythmia produced in our cases during hyperventilation.

Many of the patients were examined several times and most of them showed the same type of disturbance in the repeated examinations, in two cases, however, the findings were not constant. The effect of sedation on the above findings was not studied.

Quantitative studies on the amount of hyperventilation were not possible in the entire series. Even though all the patients cooperated well, by breathing deeply and rapidly, variations in the total volume of air respired, of course, existed. It was our impression, however, that if abnormal activity appeared, it did so before 180 seconds of hyperventilation, or not at all. In an attempt to confirm this, we measured with a Benedict Roth Metabolism Apparatus (made by Warren E. Collins, Inc.) the total amount of respired air during hyperventilation in three known epileptics and in three normals (table 2). One of the epileptics, breathing at a rate of 18.7 liters per minute, developed outbursts of the high amplitude, slow waves after two minutes or after having breathed 37.4 liters of air. Another epileptic, breathing 33.1 liters per minute, developed the epileptic activity after 80 seconds or after having breathed approximately 44 liters of air. The third epileptic, breathing 54.4 liters per minute, developed the first outburst of abnormal activity after one minute.

When the normals were examined, the findings were quite different. One hyperventilated 136.5 liters in five minutes, or 27.3 per minute, another 291 liters in five minutes, or 58 liters per minute, and a third 132.1 liters in

TABLE II

Effect of Hyperventilation in Producing Epileptic Dysrhythmia

Dysrhythmias were induced in the epileptics with relatively little hyperventilation, while no significant change resulted from much longer hyperventilation in normals

	Duration of Hypervent	Liters per Minute	Total Respired Air	Result
Epileptic				
1	120 sec	18.7	37.4	+
2	80 "	33.1	44.0	+
3	60 "	54.4	54.4	+
Normals				
1	300 sec	27.3	136.5	0
2	300 "	58.0	291.0	0
3	262 "	30.2	132.0	0

4⅓ minutes, or 30.2 liters per minute, and none showed any significant change in the records

While not conclusive, the above findings indicate that it is not merely the overbreathing which is responsible for the appearance of the abnormal activity we have found. It would appear that there must be an additional factor of predisposition to dysrhythmia.

It is not surprising to find in grand mal epilepsy, a dysrhythmia similar to that seen in petit mal, for certainly from the clinical standpoint, they are closely related. The facts that the two conditions so frequently occur together and that one frequently replaces the other, and that their response to medication is so similar, have led to the clinical recognition of their being different manifestations of a single disorder. That such dysrhythmias occur, however, in other conditions casts serious doubt upon the specificity of the findings in epilepsy.

That there might be some relationship between epilepsy and the other conditions showing similar disturbances in the electroencephalogram was considered, but a careful analysis of our findings produced no evidence which would support such a hypothesis. It would seem then, that what has in the past been considered a specific epileptic dysrhythmia, is, in reality, one of the common modes of electroencephalographic expression of a physiological disturbance in the brain. The variety of conditions in which this disturbance becomes manifest seems to indicate the absence of any one pathological basis for the disturbance. Jung,⁷ apparently of the same opinion, stated that a reliable differentiation between idiopathic and symptomatic epilepsy was not possible.

By what method hyperventilation releases the dysrhythmia, and what the significance of the dysrhythmia is, we do not know. We are confronted, however, with the fact that hyperventilation causes the appearance of dysrhythmia in some and not in others.

Two additional factors must be considered: (1) the degree of Z_{cbral} in the blood CO_2 produced in an individual by a specific amount

epilepsy,

breathing, and (2) the sensitivity of the brain cells to the change in blood CO_2 . It would seem that those patients who have either a disturbance in the regulatory mechanism of blood CO_2 with normally functioning brain cells, or damaged brain cells which are abnormally responsive to changes in blood CO_2 in the presence of a normal regulatory mechanism, are apt to develop the same dysrhythmia during hyperventilation.

After having found abnormal concentrations of blood CO_2 in epileptics, and after having observed that the chemical changes in the blood induced by hyperventilation differed in patients with petit mal from those in normals, Gibbs, Lennox and Gibbs suggested that idiopathic epilepsy might be the result of a disturbed regulation in blood CO_2 . A similar disturbed physiology may also exist in the relatives of the patients with epilepsy and chorea and in the patients with migraine who showed identical dysrhythmias during hyperventilation. While this same mechanism may be at work in the patients with organic brain disease who showed the same abnormality in their electroencephalograms during hyperventilation, there is a great likelihood that the damaged cortical cells are unusually sensitive to normal changes in the blood CO_2 . This certainly appears to be the case in those patients where the outbursts of high amplitude, slow waves were confined to, or predominated in, the area around the lesion.

We have subjected a group of children without any known disease of the brain to hyperventilation and have obtained records in a large number of them which are not distinguishable from those seen in epileptics. We do not know whether this is the result of abnormal fluctuations in blood CO_2 during hyperventilation or increased sensitivity of the cortical neurons in connection with the patients' ages.

Concerning the significance of the dysrhythmia, we feel that it may be a regression to a more primitive type of cortical activity. There are many facts in support of this. The electroencephalogram of infants is characterized by slow activity. As cortical activity differentiates and matures, the gross synchronization of large groups of cells becomes more and more interrupted, giving rise to an increasing number of independently functioning smaller neuronal pathways and discharges, transforming a rhythm of three to four per second to a ten per second activity that characterizes the adult record. When the normal physiology of the brain is disturbed by spontaneous or induced abnormal fluctuations in the blood chemistry, or when a diseased brain becomes unusually hyper-sensitive to normal variations in a blood chemistry, a more primitive activity appears. It is analogous to the clinical observation that the newly acquired functions of the cortex are lost first when the cortex becomes diseased. It is interesting to note that Blake,

Ward and Kleitman⁶ reported the occurrence of high amplitude, slow waves which are similar to those seen in epilepsy, in the stage of deep sleep. One high amplitude, slow activity and, in places, wave and spike formations as described by Hoagland and his co-workers⁷ in the electroencephalogram of dogs anesthetized with nembutal. Adults in states of impaired

consciousness show slow activity, and it may be significant that children without brain disease are much more prone to develop the dysrhythmia than normal adults. We feel that this may be an important factor aside from the encephalitis in the obtaining of such a high percentage of abnormal records in the children with Sydenham's chorea.

The results of this study in themselves, as can be seen, leave many questions unanswered. They do, however, seem to indicate that the dysrhythmia seen in epilepsy is not specific for that condition, and suggest that the tendency to dysrhythmia may be related to age as well as to heredity.

SUMMARY AND CONCLUSIONS

1 The electroencephalographic changes during hyperventilation were studied in 50 epileptics and compared with the findings in 50 non-epileptics.

2 It was found that the dysrhythmia which is observed in idiopathic epilepsy occurs in other conditions associated or not with a convulsive state, and, therefore, cannot be considered as pathognomonic of the convulsive state. The occurrence of the dysrhythmia in adults, however, cannot be considered normal.

3 Hyperventilation can exaggerate an already existing dysrhythmia or release a latent dysrhythmia.

4 There is some indication that the tendency to dysrhythmia is related to age as well as heredity.

REFERENCES

- 1 GIBBS, F. A., DAVIS, H., and LENNOX, W. G. The electroencephalogram in epilepsy and in conditions of impaired consciousness, *Arch Neurol and Psychiat*, 1935, **xxiv**, 1133-1148.
- 2 LENNOX, W. G., GIBBS, F. A. and GIBBS, E. L. Effect on electroencephalogram of drugs and conditions which influence seizures, *Arch Neurol and Psychiat*, 1936, **xxvi**, 1236-1250.
- 3 JASPER, H. H., SOLOMON, P., and BRADLEY, C. Electroencephalographic analysis of behavior problem children, *Am Jr Psychiat*, 1938, **xcv**, 641-658.
- 4 COBB, S., SARGANT, W. W., and SCHWAB, R. S. Simultaneous respiratory and electroencephalographic recording in cases of petit mal, *Arch Neurol and Psychiat*, 1939, **xlii**, 1189-1191.
- 5 OSGOOD, R., and ROBINSON, L. J. Cessation of epileptic seizures and the electroencephalogram, *Arch Neurol and Psychiat*, 1940, **xliii**, 1007-1008.
- 6 GIBBS, E. L., LENNOX, W. G., and GIBBS, F. A. Variations in the carbon dioxide content of the blood in epilepsy, *Arch Neurol and Psychiat*, 1940, **xliii**, 223-239.
- 7 JUNG, R. Electroencephalographic findings in epilepsy and related conditions, *Arch f Psychiat*, 1939, **cix**, 335-338.
- 8 BLAKE, H., GERARD, R. W., and KLEITMAN, N. Factors influencing brain potentials during sleep, *Jr Neurophysiol*, 1939, **ii**, 48-60.
- 9 HOAGLAND, H., HIMWICH, H. E., CAMPBELL, E. H., FAZEKAS, J. F., and HADIDIAN, Z. Effects of hypoglycemia and pentobarbital sodium on electrical activity of cerebral cortex and hypothalamus (dogs), *Jr Neurophysiol*, 1939, **ii**, 276-288.
- 10 SCHWAB, R. S. Method of measuring consciousness in attacks of petit mal epilepsy, *Arch Neurol and Psychiat*, 1939, **xl**, 215-217.

CERTAIN INFECTIONS IN THE BACKGROUND OF PATIENTS WITH CORONARY OCCLUSION *

By JOHN T KING, M D , F A C P , *Baltimore, Maryland*

FOR some years the question of etiology has held a fascination for many of us who are interested in the cardiovascular disorders of middle and late life. In what way do persons who experience a sudden occlusion of a coronary artery at the average age of about 60 years differ from the generality of mankind? Are they members of unfortunate families, victims of improper habits of activity or diet, or do they smoke, drink, or exercise too violently? Is the "pace of modern life" too brisk or demanding?

I confess to an inability to establish a constitutional type as a common denominator. The "high pressure" business executive or busy doctor is followed by the college professor or the clergyman. While the businessman or doctor may work too hard and smoke too much, the professor and clergyman have led lives free of unhygienic stigma. In analyzing 150 cases of coronary occlusion from his practice, Blumer¹ found that 52 per cent were total abstainers from alcohol, 34 per cent drank occasionally, 14 per cent habitually, 34 per cent smoked nothing, 36.6 per cent were moderate smokers, 30 per cent excessive.

Diabetes is a well known cause of coronary sclerosis, as it is of general arteriosclerosis, and may be incriminated as a cause of certain cases of coronary occlusion. Polycythemia is another cause of angina pectoris or coronary occlusion. However, these conditions can be held responsible for only a small proportion of the total cases.

Sex is a factor. Only one of each five cases in my practice is in a woman. It is interesting to note that some of the women affected are of the *typus masculinus*, at least as regards habits of work and play. Although such cases do occur, coronary occlusion is very rare before the age of 60 among women leading the protected life of a housewife.

Searching for a common denominator among such factors as constitution, working habits, smoking and drinking habits, heredity and exercise, has proved nothing to my satisfaction. Sex is a denominator of 80 per cent. But even supposing that all cases occurred in men, we would still lack an explanation for the occurrence of premature coronary disease in certain individuals.

For some years I have been impressed by the frequency with which I encounter the history of excessive upper respiratory infection or rheumatic fever in the background of my private patients with coronary artery disease. Fortunately, although my practice tends somewhat toward cardiovascular

* Presented before the American Clinical and Climatological Association October 16, 1941.
Received for publication October 28, 1941.

disorders, it is by no means limited. It has been driven home to me, through the constant reports of intelligent persons, that such infections are rather excessive among cases of coronary occlusion, both as regards intensity and repetition. Now, having accumulated a considerable number of cases, I am undertaking to analyze them and to compare them with proper control cases.

The literature contains many intimations regarding the infection theory, though it is not very conclusive. Gross and Oppenheimer⁶ are skeptical, reporting that "despite the rather frequent involvement of the coronary arteries during the course of acute rheumatic fever, it has not been possible to establish such an entity on clinical grounds." Perry¹² found that the coronary arteries are usually affected in rheumatic carditis, the lesion is a panarteritis, consisting of (a) intimal thickening more or less cellular, (b) degenerative and inflammatory lesions of the intima, (c) inflammatory infiltration of adventitia. Klotz¹⁰ reports the large coronary arteries to be inconstantly affected, the smaller branches very constantly, by the rheumatic infection. Christian³ holds the view that, in coronary disease, the artery is most often the seat of arteriosclerosis, while, at other times, an arteritis, possibly resulting from syphilis or bacterial infection, is found. He thinks arteritis plays an important part, especially in younger individuals who have not had syphilis.

More specifically, Jones and Rogers⁷ suspect a streptococcus in the etiology of cardiovascular disease, including coronary thrombosis. In 11 cases of death from coronary occlusion, the vessel in only one showed much narrowing due to arteriosclerosis. In the others were found fresh clots, sections showed lymphocytes, plasma cells, diplococci and short chain cocci. These organisms were found in the subintimal proliferative areas and in the outer media and adventitia. In this connection, consider the speculative hypothesis on the pathology of atheroma in the recent volume on the Biology of Arteriosclerosis by Winternitz et al.¹⁴ After a beautiful exposition of the basic pathology of atheromatous plaques, these authors point out certain features of similarity between such lesions and those found in the endocardium as a result of rheumatic infection. It is intimated that such lesions as plaques in the coronary and other arteries may result from bacterial invasion, possibly with the *Streptococcus viridans*.

Typhoid fever has been found to involve the coronary arteries. In 1930, in discussing Klotz's paper, Thayer¹³ mentioned the case of a young man dying of typhoid in his third decade of life. At necropsy, an area of endarteritis was found around one coronary artery, had this patient lived, the lesion would have led to coronary constriction and provided a favorable site for occlusion.

Newsholme¹¹ has pointed out that, while the evil effects of excessive muscular work, overfeeding, alcoholism, and excessive smoking upon the arteries are generally recognized, yet the chief damage to arteries is done by infections. He names rheumatic fever, syphilis, focal and other infections

with pneumococcus or streptococcus. Thus, clinical evidence *in re* the rheumatic infection and the coronary arteries is suggestive, but not conclusive. Evidence bearing on repeated tonsillitis as a possible factor in coronary disease is even more elusive. In 1926, Kahn⁹ reported that he had been impressed by the frequent occurrence of acute tonsillitis in the background of his private patients with angina pectoris. Of 82 patients, 24 reported having suffered repeated tonsillitis attacks, 20 gave a history of rheumatic fever, 10 were diabetics, no control cases were reported. As will be shown later, the incidence of tonsillitis in Kahn's patients (29 per cent) is not excessive, as it was reported in 34.5 per cent of my control cases (table 1). However, his figure of 20 cases with rheumatic history (24 per cent) is very high and quite suggestive.

Among my private patients have been found 157 instances of well authenticated coronary occlusion. One case of thrombo-angiitis obliterans, three of diabetes, and two of polycythemia were eliminated, 11 others were unavailable from lack of sufficient data. Thus, 140 cases are available, in none of which was there a background of any of the known or usually suspected etiologic agents.

TABLE I
Comparative Incidence of Infections (in Per Cent)

	Rheumatic Fever	Excessive Tonsillitis	Infected or Scarred Tonsils	No Evidence of Infection
Coronary Occlusion (140)	11.8	52.1	32.1	20
Controls (110)	5.0	34.5	24.5	36.4

Control Cases. For comparison, these were drawn also from my private files, histories of both the coronary cases and the controls having been taken by myself. The proportion of males to females in the coronary group was 79.3:20.7 per cent, among the 110 controls the ratio was 79.1:20.9 per cent. All patients and controls were white. No case was used as a control in which tonsil infection could be suspected as an important or, perhaps, etiologic factor, thus, all cases of rheumatic valve disease, hypertension, exophthalmic goiter, rheumatoid arthritis and nephritis were excluded. Controls were selected so that each white male and female respectively in the first 110 coronary cases was matched by a male or female of corresponding age in the control group. Comparison of the two groups in per cent is shown in table 1.

Rheumatic Fever. The proportion of 11.8 per cent of patients who gave a history of past rheumatic fever in the coronary group to 5 per cent in the control group is not very striking. However, in the coronary group were four patients with frank rheumatic valve disease, who gave no history of rheumatic fever. Including these we have 14.6 per cent of coronary cases in which either a history of rheumatic fever or rheumatic valve disease, or

both, was found. Although this is nearly three times as great as the figure for control cases (5 per cent), it is not statistically significant. It would appear that, although the number of patients with coronary occlusion who had had known rheumatic fever is suggestively high, yet the incidence of rheumatic infection is not sufficiently frequent to provide a common denominator.

Excessive Tonsillitis Of 140 patients with coronary occlusion, 73 (52.1 per cent) had experienced repeated attacks of tonsillitis or quinsy, or both, against 38 (34.5 per cent) among the control cases. Ordinary sore throats, or a single or occasional attack of tonsillitis, were ignored.

Tonsillectomy Study of the cases in which one or more operations or cauterization had been performed upon the tonsils was not fruitful. Thirty-five per cent of the coronary cases gave a history of such a procedure against 34.5 per cent of the control cases. As these operations were not done on a prophylactic theory, but for relief from chronic or acute infections, they cannot be said to provide evidence against the hypothesis that tonsillitis may affect the coronary vessels. In other words, the harm, if harm there was, could have occurred before the infection was arrested. This is especially indicated since many operations were postponed until adult or middle age.

Age Dr C. Holmes Boyd, who has been interested with me in the subject under discussion, pointed out the marked incidence of the suspected infections among the youngest patients with coronary occlusion. Though there were only six such cases in persons under 40 years of age, yet two, and probably a third, had had rheumatic fever. Five gave a history of excessive tonsillitis, and four had had tonsil operations.

Case 1 Male, aged 39. History of rheumatic fever. Tonsillectomy performed, with stump remaining in one fossa.

Case 2 Male, aged 35. History of repeated tonsillitis and cervical adenitis.

Case 3 Male, aged 39. History of rheumatic fever and repeated tonsillitis. Tonsillectomy performed at age of 35.

Case 4 Male, aged 39. No history of tonsillitis or rheumatic fever. Syphilis treated 20 years before.

Case 5 Male, aged 36. Repeated sore throats and two tonsil operations as a child. Put to bed several weeks as child for "enlarged heart and fever", no arthritis. Thought to have had rheumatic fever.

Case 6 Female, aged 38. Tonsillitis each year until age of 10, when tonsillectomy was done. Chronic antrum infection with fever over period of one year with two radical operations.

With such reports in mind, one is tempted to jump to the conclusion that, while such infections may be concerned in causing premature vascular damage in younger persons, yet it may be assumed that coronary occlusion in the upper decades of life is merely the result of more or less normal processes of aging. To test this hypothesis, patients were divided according to decades, and their histories compared with those of the control group (table 2). This concept is not supported by the comparison, since it is readily seen that

TABLE II

Incidence of Excessive Tonsillitis among Coronary Cases and Controls, by Decades
(in Per Cent)

Age	Controls	Coronary Occlusion
30-40	20	83
41-50	37	40
51-60	43	58
61-70	26	45
Over 70	25	43

the excessive incidence of tonsillitis is not limited to the background of the younger type of patient, it is found at any age. The rather low figure for coronary patients in the fifth decade is difficult to explain.

Clear Histories It is possible to approach the question from the negative viewpoint, selecting only those cases in which none of the suspected infections was indicated. Thus, certain persons gave no history of excessive tonsillitis, quinsy, or rheumatic fever, showed no evidence of past or present tonsil infection when examined, and had had no operative procedures on the throat. Forty (36.4 per cent) of the control cases fall into this category, against 28 (20 per cent) of those who had had coronary occlusion.

DISCUSSION

To demonstrate a relationship between the suspected infections and coronary occlusion, it must be shown that the infections have been significantly higher in the background of patients with this disorder than among properly selected controls. As stated above, every precaution was taken to match control cases with cases of coronary occlusion, male with male, female with female, age with age. Since we are testing the possible effects of repeated tonsillitis, all cases of diseases in which tonsillitis is suspected of being concerned had to be excluded from the group of controls. Thus, cases of rheumatic valvular disease were excluded. It may be argued that it is not fair to include cases of rheumatic valve disease in the coronary occlusion group, while excluding them from the controls. This point needs discussion.

Among the 140 cases of coronary occlusion, 16 gave a history of past rheumatic fever, while one was thought to have had rheumatic fever. The one probable case was listed as one-half, raising the number to 16.5 (11.8 per cent). In addition to these were found four cases of frank rheumatic valve disease among the coronary cases, in which no history of rheumatic fever was obtained. Thus we have 20.5 cases, or 14.6 per cent, of the coronary group in which the history or valve disease, or both, gave evidence of previous rheumatic infection. Against this figure, 5 per cent of the control group gave a history of previous rheumatic fever. But we have excluded cases of rheumatic valve disease from the control group because of the known relationship between tonsillitis and rheumatic fever. Thus, the

control group may be a superior group rather than an ordinary healthy group. What is the incidence of rheumatic valve disease in the community at large? In other words, how many cases of rheumatic valve disease must be added to the control group to make it comparable with the universe of human beings? In Philadelphia, Cahani² has estimated that about 1 per cent of 350,000 school children have some form of heart disease, and that

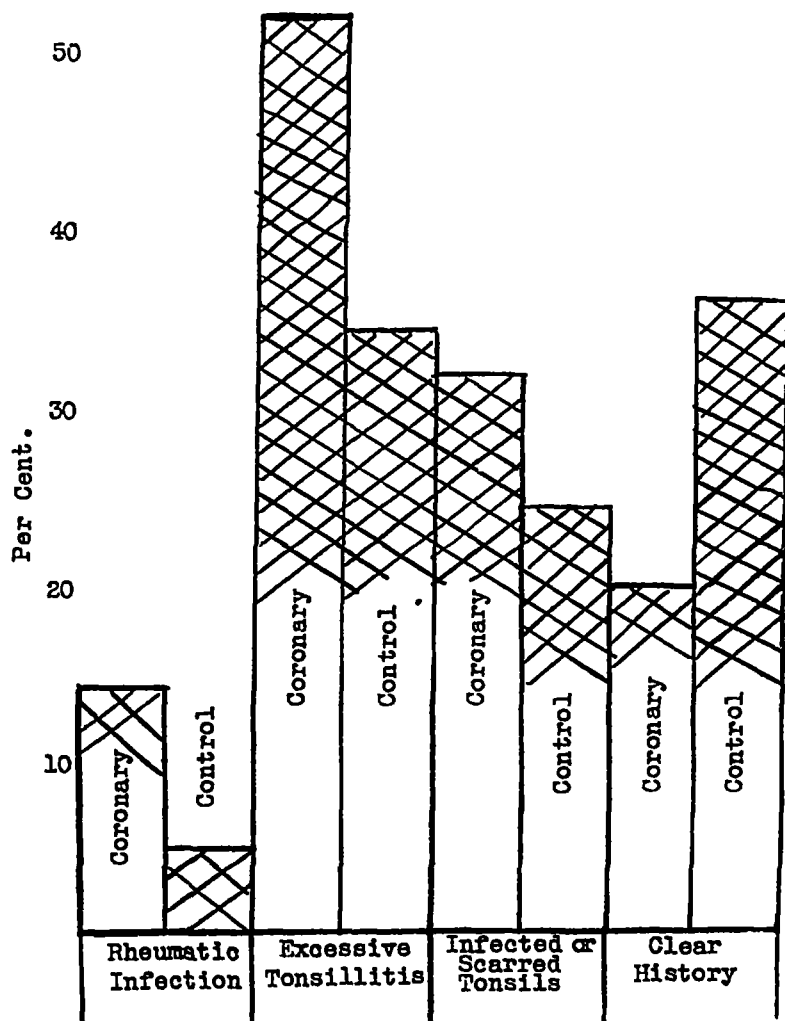


FIG 1 Incidence of rheumatic and tonsillar infections among cases of coronary occlusion and control cases, in per cent

rheumatism accounts for most cases. This is the best evidence I have found on the incidence of rheumatic heart disease in a climate similar to that of Baltimore.

The two groups may be compared as follows, with regard to rheumatic infection. Coronary group: positive history in 11.8 per cent plus valvulitis without history in 2.8 per cent = 14.6 per cent. Control group: positive his-

tory in 5 per cent plus (probable incidence of valvulitis in community, but excluded from control group) 1 per cent = 6 per cent

Now, these numbers are not large, and the results not very convincing. Rheumatic infection as commonly regarded can not be considered a common denominator in the etiology of coronary artery disease. Nevertheless, the incidence of positive histories (11.8 per cent) is suspiciously high for a group derived from private practice, as is also the incidence of rheumatic valvulitis. It is conceivable that coronary disease in a person who has had rheumatic infection is due, not to rheumatic fever, but to the tonsillitis that often afflicts the rheumatic patient.

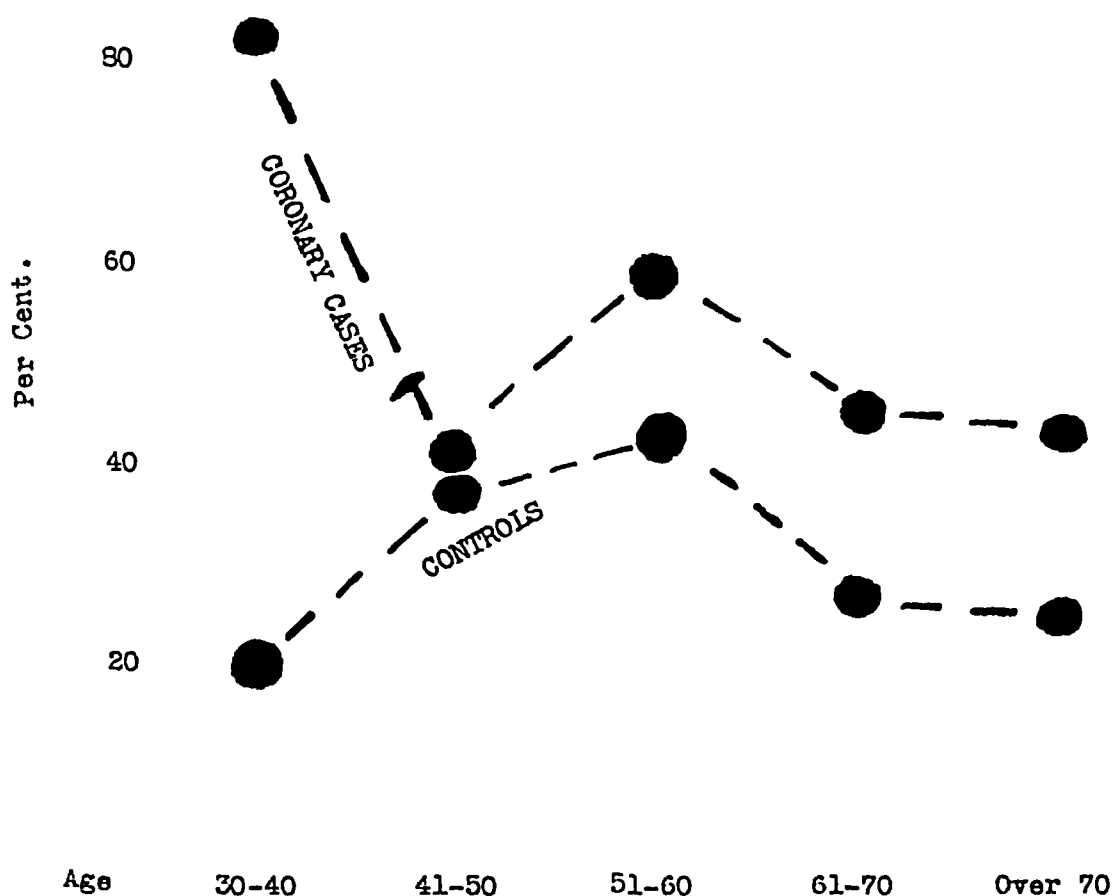


FIG. 2 Graphic representation of incidence of excessive tonsillitis among control cases and patients having coronary occlusion, arranged by decades

Other Infections It is hardly necessary to consider tuberculosis or syphilis very seriously as important causes of coronary occlusion. Occasional cases of angina or of coronary occlusion are found due to encroachment of a syphilitic aortitis upon the coronary orifices. However, these cases constitute a small proportion of the total instances of coronary occlusion in private, and even in hospital, practice. Tuberculosis is not a factor.

In analyzing my cases, I found that 12 of 140 patients (8.6 per cent) gave a history of previous typhoid fever. Since the age of all patients with

coronary occlusion is such that they have lived through a period of enormous epidemics of typhoid, such a morbidity figure does not seem excessive. It must also be remembered that Baltimore, where many of these patients have lived for years, held at times the record for the highest incidence of typhoid in the country.

Among the coronary cases, the history of previous pneumonia occurred only a few times, while malaria was even less common.

Many patients in both the coronary group and among the controls had sinus infection or treatment directed at the sinuses. It is very difficult for an internist to estimate the importance of such infections. Although it is reasonable to suppose that serious sinus infections may cause systemic damage in the form of arterial disease, I have found it impossible to arrive at satisfactory evidence.

Tonsillitis Reliability of histories may be considered high, since all cases in both the coronary and control groups were drawn from my private files. The results are not ideal. Patients suffering from acute tonsillitis may report an ordinary sore throat or no sore throat at all. Others give a completely negative history while presenting obviously infected or heavily scarred tonsils. To balance such errors, the same methods of history-taking and examination were also applied to the control cases.

Is the difference in the incidence of tonsil infection in the two groups sufficient to be significant? In other words, is it likely that the difference between 52.1 per cent of excessive tonsillitis in the coronary group as against 34.5 per cent in the control group (17.6 per cent), is due merely to chance? Here we can apply the formula in common use for determination of the *standard deviation of the difference*, i.e., the scattering of figures that might be considered due to sampling, or the laws of chance. The total figures involved are

Coronary cases with excessive tonsillitis	73
Coronary cases without excessive tonsillitis	67
Total	140
<hr/>	
Control cases with excessive tonsillitis	38
Control cases without excessive tonsillitis	72
Total	110
<hr/>	
Total cases in 2 groups	250
Total cases with excessive tonsillitis	111
Total cases without excessive tonsillitis	139

The formula for determining the standard deviation of the difference is

$$\sqrt{\frac{PQ}{N_1} + \frac{PQ}{N_2}}^*$$

* Dr. Margaret Merrell, of the School of Hygiene and Public Health, Johns Hopkins University, was kind enough to advise me regarding this formula.

in which

$$P = \text{proportion of positive cases} = \frac{111}{250}$$

$$Q = \text{ " " negative " } = \frac{139}{250}$$

$$N_1 = \text{number in coronary group} = 140$$

$$N_2 = \text{ " " control " } = 110$$

Thus

$$\sqrt{\frac{\left(\frac{111}{250}\right)\left(\frac{139}{250}\right)}{140} + \frac{\left(\frac{111}{250}\right)\left(\frac{139}{250}\right)}{110}}$$

The result is 6.3 per cent. Ratio of observed difference to standard deviation of the difference $17.6/6.3 = 2.8$

It is common practice in statistical work to consider that a difference in proportion is probably significant if it proved to be two or more times as great as the standard deviation of the difference. We are dealing always, however, with probabilities and not with established fact. Hill¹⁵ states that, when the observed difference is 2.5 or 3 times the standard error, then "differences would occur by chance, roughly, only once in 80 tests and once in 370 tests". As our figure (2.8) lies between the two, it is quite unlikely that it is due to chance.

In table 1 it is shown that 20 per cent of the coronary cases gave no history of excessive tonsillitis or of tonsillectomy, and presented no evidence of infection on examination. This contrasts with 36.4 per cent of the control group. The observed difference is 16.4 per cent. Is this figure statistically significant? Applying the same formula used above, we find that the standard deviation of the difference in the two groups is 5.7 per cent. The ratio of observed difference to standard error is $16.4/5.7 = 2.9$. This figure, then, is quite high and almost assures (V S) that the difference of clear histories in the two groups is not due to chance.

It can not, of course, be said that frequent tonsillitis is necessarily the cause of coronary disease, even if the relationship between tonsillitis and coronary occlusion is a close one from the statistical standpoint. Such a relationship might be explained on the ground that certain persons are of vulnerable constitution and susceptible to both conditions. And what of the many persons who have frequent tonsillitis and who escape cardiovascular damage? The last is hardly pertinent in itself, for innumerable persons suffer repeated tonsillitis and escape rheumatic fever and rheumatic valvulitis, yet the importance of tonsillitis in these states can hardly be questioned.

In recent years a number of investigators (V S) have advanced evidence to suggest that some sort of infection may be responsible for coronary artery disease. One of the weak links in the chain of proof has been the lack of clinical evidence to show that such infections do occur, and the lack of proof of the nature of such infections. My own impressions were obtained before

the publication of the pathologic and bacteriologic work referred to above. We are still in need of more clinical reports of the type I am attempting here.

CONCLUSIONS

1 Excessive tonsillitis occurs in the background of patients with coronary occlusion in a degree of frequency that is beyond reasonable statistical doubt.

2 It is possible that the rheumatic infection should also be suspected as a possible cause of coronary artery damage.

BIBLIOGRAPHY

- 1 BLUMER, G. Letter to the editor, *Jr Am Med Assoc*, 1934, cii, 1177.
- 2 CAHAN, JACOB M. Rheumatic heart disease in Philadelphia school children, *ANN INT MED*, 1937, x, 1752.
- 3 CHRISTIAN, H. A. Diagnosis and treatment of diseases of the heart, *Oxford Monographs on Diagnosis and Treatment*, 1928, iii, 260.
- 4 DAVIS, D., and KLAINER, M. J. The role of hypertension per se in the development of coronary sclerosis, *Am Heart Jr*, 1940, xix, 193.
- 5 GROSS, H., and OPPENHEIMER, B. S. The significance of rheumatic fever in the etiology of coronary artery disease and thrombosis, *Am Heart Jr*, 1936, xi, 648.
- 6 GROTEL, D. M., et al. Etiologic factors in atherosclerosis of 134 cases, *Klin Med, Moscow*, 1940, xviii, 34. (Trans and Abstr in *Jr Am Med Assoc*, 1940, v, 114.)
- 7 JONES, N. W., and ROGERS, A. L. The incidence of streptococcal infection in cardiovascular sclerosis, *ANN INT MED*, 1935, viii, 834.
- 8 JONES, N. W., and ROGERS, A. L. Chronic infections and atherosclerosis, *Med Jr Australia*, 1939, i, 851.
- 9 KAHN, MORRIS H. Etiologic factors in angina pectoris, an analysis of 82 cases in private practice, *Am Jr Med Sci*, 1926, clxxii, 195.
- 10 KLOTZ, OSKAR. Rheumatic fever and the arteries, *Trans Assoc. Am Phys*, 1912, xxvii, 181.
- 11 NEWSHOLME, SIR ARTHUR. National changes in health and longevity, *Pub Am Statist Assoc*, 1920-21, xvii, 689.
- 12 PERRY, C. B. The main branches of the coronary arteries in acute rheumatic carditis, *Quart Jr Med*, 1929-30, xxiii, 241.
- 13 THAYER, W. S. Discussion, *Trans Assoc Am Phys*, 1930, xlv, 167.
- 14 WINTERNITZ, M. C., THOMAS, R. M., and Lecompt, P. M. The biology of arteriosclerosis, 1938, C. C. Thomas, Springfield, Ill.
- 15 HILL, A. BRADFORD. Principles of medical statistics, 1937, The Lancet Ltd, London.

HETEROPHILE ANTIBODY REACTION CAUSED BY BACTERIAL INFECTION*

By S BORNSTEIN, M D , *New York, N Y*

A HUMAN serum was found to contain a high titer of heterophile antibodies even though the patient suffered neither from serum sickness nor from infectious mononucleosis (so-called false Paul-Bunnell reaction). This observation and the results obtained from the study of the antibodies involved, seem to be worth reporting because such reactions are very rare. Also, for the first time, it was possible in this case to explain the serological phenomenon on the basis of an infection with a bacterium containing heterophile antigen.

Sheep hemolysins and agglutinins occurring after immunization with an antigen which is present in the tissues of various animals are called Forssman antibodies¹. The Forssman hemolysins can be easily differentiated from homologous sheep hemolysins by the fact that the former do not act on ox cells, while the latter do. Friedemann² examined the so-called normal sheep hemolysins occurring in human sera and found them to be of the Forssman type. He introduced the name "heterophile" for such antibodies in general, a designation which has become widely accepted. Therefore the term Forssman antibody should be used only for anti-sheep bodies which fully correspond to the well-defined Forssman antigen in the guinea pig kidney or to similar tissue antigens.

Increase in the titer of sheep antibodies in human serum was observed by Hanganutziu³ and Deicher⁴ after injection of animal serum and by Paul and Bunnell⁵ in cases of infectious mononucleosis. Mainly through the work of Davidsohn⁶ and Stuart and co-workers⁷ routine methods were introduced for differentiation of the three types of heterophile antibodies in human blood, namely the "normal" anti-sheep bodies, those found after serum injections, and the heterophile antibodies occurring in infectious mononucleosis.

Stuart and co-workers in cases of meningococcus meningitis complicated by serum sickness found heterophile antibodies, at least part of which behaved like the type of antibodies encountered in infectious mononucleosis. Solner and co-workers⁸ observed a titer of 1:160 for sheep cell agglutinins in the serum of a patient who apparently suffered from infectious mononucleosis. This agglutinin could be absorbed with guinea pig kidney and was present in the patient's serum only in the first of four tests made between the third and the twenty-ninth days after the onset of the illness. The authors

* Received for publication June 24, 1941.

From the Department of Bacteriology and Serology, Beth Israel Hospital, New York,

Aided by a grant from the Ella Sachs Plotz Foundation.

drew attention to the fact that the patient had received treatment with a sulfonamide compound a few days before. It seems very unlikely that any correlation can be established between this medication and this very unusual serological finding. Warren,⁹ quoting Sohler's observation, contended that the titer of normal heterophile antibodies (of the Forssman type) may be increased before or simultaneously with the appearance of the antibodies of infectious mononucleosis. Beer¹⁰ questioned the usefulness of absorption of sheep agglutinins with ox cells. He compared the action of different types of heterophile antibodies on the blood of various animal species and concluded that at least part of the antibodies occurring after serum injection are identical with the normal anti-sheep bodies of the Forssman type.

Thus the differentiation of the three types of heterophile antibodies in human serum has become more involved, but their separate occurrence remains an established fact. In general, it can be stated that the titer of the normal heterophile antibodies is low, with a maximum for sheep cell agglutinins around 1:50, and that marked increase in titer is due to previous serum injection or to infectious mononucleosis. Few exceptions from this rule are recorded.

In 1931, Fischer¹¹ found that the serum of a patient who apparently had suffered from gonococcus septicemia contained a strong sheep cell agglutinin. No titer was given, nor were absorption experiments carried out. Paul and Bunnell⁵ reported a high titer of heterophile antibody in the serum of a patient in the terminal stage of aplastic anemia with high fever. De Vries¹² saw a positive heterophile antibody reaction (1:128) in a case of scarlet fever and reported that Minkenhof had found "unexplained high titers in rubeola, tuberculosis and filariasis."

Bernstein,¹³ stating that high titer heterophile antibody reactions not due to serum injection or infectious mononucleosis are "excessively uncommon," mentioned that parenteral administration of liver extract may produce titers as high as 1:1280. Bernstein has not yet reported this observation in detail.

It is surprising that increased titers of heterophile antibodies are not observed more frequently, because it has been shown that an ever increasing number of bacteria contain heterophile antigen. Among these bacteria are the Shiga bacillus and several pneumococcus and Salmonella types. Bailey¹⁴ proved that not only injection of dead antigen preparations from such bacteria can increase the heterophile antibody titer in experimental animals, but that there is a relation between infection with *Past. leptiseptica* and increased heterophile antibody titer in rabbits. Bailey and Shorb¹⁵ reported an increase of sheep hemolysins in the serum during the course of pneumonia. Hedén¹⁶ saw the same in gonorrhea. Though he could not demonstrate heterophile antigen in gonococci, he quoted Bailey who found it, at least in one strain.

From these facts, it is apparent that there is some relation between heterophile antibody titer in human sera and infections. This relation is shown more clearly by the following case:

CASE REPORT *

N C, a 28-year-old white male, was admitted to this hospital on November 24, 1940. He had had urinary frequency, urgency and nocturia for 1½ years, after an upper respiratory infection, and for six months he had been complaining of abdominal pain in the right upper quadrant. Five days before admission he had taken castor oil and following that felt weak and had bloody stools. There was no history of injection treatment of any kind within many years. On admission he was severely anemic, his blood contained 1.9 million red blood cells and 32 per cent hemoglobin, the white blood count on November 25 was 6,600 leukocytes, the differential count showed 1 basophile, 5 staffs, 59 segmented polymorphonuclear neutrophils, 31 small lymphocytes, 4 monocytes. There were occasional red and white blood cells in his urine. The diagnosis was bleeding duodenal ulcer and contracture of the bladder neck. The treatment consisted of blood transfusions, vitamins and Meulengracht diet. The patient's temperature varied between 99° and 103° and went to 106° on November 28. At this time a blood culture was taken and contained *E. coli*, 20 colonies per c.c. During the following night the temperature reached 107.5°. Signs of severe cystitis were present. Introduction of a permanent catheter brought relief. The white blood count on November 29 was 15,900 leukocytes, 16 staffs, 78 segmented polymorphonuclear neutrophils, 5 lymphocytes, 1 monocyte. The urine contained staphylococci, streptococci, *Ps. pyocyanea* and *E. coli*. Sulfathiazole was given from November 28 until December 1. The patient's temperature came down to normal within a week. Blood cultures taken subsequently were sterile. Liver extract was given by injection for the first time on December 4. After his gastric condition had improved, the patient was transferred to the genito-urinary service where transurethral resection of the neck of the bladder was performed. He was discharged, very much improved, on January 15, 1941.

Serological Findings On November 26, 1940, serum for a Wassermann test was obtained. The result of the examination was Wassermann positive, Kahn and Kline tests doubtful. Repetitions on December 1, 4 and 12 Wassermann positive, Kahn and Kline tests negative. On December 31, 1940, and on April 10, 1941, when the patient was seen in the follow-up clinic, Wassermann, Kahn and Kline tests were negative.

The serum obtained on December 1 agglutinated the colon bacillus from the patient's blood up to a dilution 1:400. Among 10 strains of *E. coli* isolated from different cultures of the patient's urine none was serologically identical with the strain from the blood.

The serum specimen obtained on December 1 for a Wassermann test was first examined for sheep cell agglutinins on December 6 and gave agglutinations up to 1:1600 final serum dilution. The hemolytic titer was determined on December 10 and found to be 1:20000 (dilution of serum completely hemolysing an equal volume of 5 per cent sheep cell suspension in the presence of complement).

Serum obtained on December 11 was immediately examined for heterophile antibodies. It agglutinated sheep cells up to a dilution 1:200, the hemolytic titer was 1:2000. On December 15 the antibody content of the patient's serum had already reached the upper border of normal values and decreased further subsequently as may be seen from the chart (table 1).

The patient belonged to the blood group O. The α -agglutinin in the serum specimen of December 1 had a titer of 1:800. It decreased to 1:100 by December 11, remaining at this level throughout the observation.

On December 17 and 19 the two serum specimens obtained on December 1 and 11 were absorbed with 20 per cent suspensions of boiled ox cells and guinea pig kidney, using Davidsohn's technique (slightly modified). On this occasion it was noticed that the older serum specimen had lost three-fourths of its agglutinin and a large part of the

* Clinical data obtained by courtesy of Drs H. A. Rafsky and A. Hyman.

TABLE I

Patient N.C.																						1941	
1940		Dec.																				1941	
Nov.																						Jan.	
24 25 26 27 28 29 30		1 2 3 4 5 6 7		8 9 10 11 12 13 14		15.....		26 ...31														Apr.	
Temperature																							
Transfusions																							
Sulfathiazole																							
Inject. of liver extract																							
Blood cultures																							
Wassermann																							
Kahn																							
Kline																							
Titers of sheep cell agglutinin																							
" hemolysin																							
isoagglutinin anti-A																							
agglutinin for E.coli N.C.																							

hemolysin during storage in the ice box. However, the remaining antibodies (sheep cell agglutinin 1:400, hemolytic titer 1:2000) and the ones in the more recent serum specimen showed the same behavior, namely the heterophile antibodies could be absorbed with guinea pig kidney, but not with ox cells (table 2).

TABLE II
Serum N C 12/1

		Before Absorption	After Absorption		
			With G P Kidney	With Ox Cells	
Hemolytic titer (0.25 c.c. serum in dil., 0.25 c.c. 5% sheep cells, 0.25 c.c. complement 1:10, 20' at 37°)	Serum dilution				Serum D W 12/19 (infectious mononucleosis)
	1:250	c	o	c	
	1:500	c	o	c	
	1:1000	c	o	c	
	1:2000	c	o	c	
	1:4000	1	o	1	
	1:8000	o	o	o	
Sheep cell agglutination (0.3 c.c. serum in dil., 0.3 c.c. 1% sheep cells, after 10' at room temp centrifuge, shake and read)	Final dilution of serum				Before Abs
	1:25				+
	1:50				+
	1:100	+	-	+	+
	1:200	+	-	+	+
	1:400	+	-	+	+
					Abs with Ox Cell
					(+)
					-
					-
					-
					-

c = complete hemolysis o = no hemolysis 1 = intermediate (partial hemolysis)
+ = agglutination - = no agglutination (+) = weak agglutination

The titer for sheep cell agglutinins in the serum specimen of December 11 also diminished during storage in the ice box, and on January 7 was positive 1 50, weakly positive 1 100 Serum of a patient with infectious mononucleosis (D W) was obtained on December 19 and stored under fully identical conditions The titer was not changed when examined last, more than six months after the specimen was taken

TABLE III
Flocculation Test
(0.2 c.c. serum in dilutions, 0.2 c.c. alcohol. extract, 37° C over night)

Serum-dil	Sheep Cell	Ox Cell	Horse Cell	Guinea Pig Kidney Extract
		Serum N C 12/11		
1 2	+++	—	—	++++
1 4	+	—	—	+
1 8	+	—	—	+
1 16	—	—	—	(+)
		Serum D M 1/14 (infect mononucleo, heterophile antibody react 1 200)		
1 2	—	—	—	—
1 4	—	—	—	—
1 8	—	—	—	—
1 16	—	—	—	—
		Forssman-rabbit serum No 20		
1 2	++++	—	—	+++
1 4	+++	—	—	+++
1 8	++	—	—	++
1 16	+	—	—	+

The flocculation test with alcoholic blood cell and organ extracts as described by Schiff¹⁸ was done on January 15 with the serum specimen of December 11 There was flocculation with the extracts of sheep cells and guinea pig kidney, but none with ox cells and horse cells The reaction was similar to one obtained with a Forssman rabbit serum Serum of a patient with infectious mononucleosis, D M of January 14, which had a sheep cell agglutination titer of 1 200, gave no such flocculation (table 3)

TABLE IV
Hemolysis Inhibition Experiment

Rabbit serum No 199 (after immunization with *E. coli* N C) three hemolytic doses, 0.25 c.c. 5% sheep cells, 0.25 c.c. complement 1 10, 0.5 c.c. of bacterial extracts in dilutions (24 hours' growth on agar slants washed off with 4 c.c. saline solution, heated at 60° C for 30', centrifuged, supernatant fluid used), 37° C —30'

Dilutions	<i>E. coli</i> N C	Extract from <i>E. coli</i> No 1737
1 5	o	c
1 10	o	c
1 20	o	c
1 40	ao	c
1 80	wk	c
1 160	ac	c

c—complete hemolysis
ac—almost complete
wk—weak
ao—almost no hemolysis
o—no hemolysis

Seven rabbits were immunized with the culture of *E coli* obtained from the patient's blood, partly with organisms killed at 60° C, partly with suspensions of living organisms or both. Four of these rabbits showed an increase of sheep hemolysins after the immunization. It could be seen that all rabbits which had had no A substance in their serum and were injected with live organisms, had responded with formation of heterophile antibodies. In the hemolysis inhibition experiment an extract of the organisms showed strong inhibition, while an identical extract of a strain of *E coli*, picked at random, failed to inhibit (table 4).

DISCUSSION

In all likelihood *E coli* had entered the patient's blood stream from the bladder wall. The regularity with which injection of living organisms of this strain caused an increase of sheep hemolysins in suitable experimental animals, and the inhibition of such hemolysins by an extract prepared from the culture, demonstrated the presence of heterophile antigen in this strain. Several authors had previously examined *E coli* for heterophile antigen, but had obtained only negative results with all their strains. The heterophile antibody reaction of the patient's serum must be explained as the result of an immunization with the heterophile antigen contained in the *E coli* strain as cultured from his blood. Infectious mononucleosis could be excluded from the clinical data. The patient had received neither a serum injection nor parenteral liver extract previous to the positive reaction. The antibodies could be absorbed with guinea pig kidney but not with ox cells, therefore they were of the Forssman type similar to the heterophile antibodies found in normal sera. The high titer of hemolysins in comparison to the titer of agglutinins is also characteristic of Forssman-like antibodies.

It has been stated repeatedly that sera from patients with infectious mononucleosis can be stored in the ice box for years without losing their antibody titer. The antibody encountered in this case partly disappeared from the specimens on standing in the ice box. Antibodies of such lability have been described before (by Kohn-Speyer¹⁹).

For the identification of heterophile antibodies of not very high titer, the flocculation test, as suggested by Schiff, proved to be of great value in this case. The increased anti-A titer at the height of the immunization effect reminds one of Davidsohn's observation of very high isoagglutinin titers in many patients with serum sickness.²⁰

Non-specific Wassermann reactions, as found in our case, are known to occur in different infections, notably in infectious mononucleosis. There seems to be no direct connection between these reactions and the occurrence of the heterophile antibodies of infectious mononucleosis. The coincidence of such a Wassermann reaction with a heterophile antibody reaction of a different type is noteworthy but does not offer an explanation for its meaning.

The fact that heterophile antibodies appear faster and also disappear more quickly from the blood than bacterial agglutinins has been pointed out. This difference is striking in this case where both antibodies were produced by an infection with the same bacillus.

SUMMARY

A strain of *E coli* cultured from the blood of a patient with severe cystitis contained heterophile antigen. Following the bacteremia the patient's serum gave a positive heterophile antibody reaction (1:1600). The antibodies could be differentiated from the ones observed in serum sickness and in infectious mononucleosis, and were of Forssman type. They disappeared rather quickly from the patient's blood and vanished partly from serum specimens kept in the ice box, unlike the antibodies of infectious mononucleosis. The Wassermann reaction was positive for some time, and there was a temporary increase of isoagglutinins.

CONCLUSIONS

It is known from animal experiments that infection with bacteria containing heterophile antigen can increase the titer of heterophile antibodies in the serum. The same can happen in man. Though the increase in antibody titer is ordinarily of minor degree, it can become very marked. The quick disappearance of the antibodies from the blood and their lability in the specimen may account, at least in part, for the rarity with which heterophile antibody reactions of this kind are observed. The antibodies in such cases are of the same type as those encountered in normal sera, which makes it probable that there is a relation between the fluctuating titers of these antibodies and infections.

REFERENCES

- 1 FORSSMAN, J. Die Herstellung hochwertiger spezifischer Schafhaemolysine ohne Verwendung von Schafblut, *Biochem Ztschr*, 1911, xxvii, 78-115.
- 2 FRIDEMANN, U. Ueber heterophile Normalamboceptoren. Ein Beitrag zur Lehre von der Entstehung der normalen Antikörper, *Biochem Ztschr*, 1917, lxxx, 333-356.
- 3 HANGANULTZIU, M. Hémagglutinines hétéro-génétiques après injection de serum de cheval, *Compt rend Soc de biol*, 1924, xci, 1457-1459.
- 4 DFICHER, H. Ueber die Erzeugung heterospezifischer Haemagglutinine durch Injektion artfremden Serums, *Ztschr f Hyg u Infektionskr*, 1926, cvi, 561-579.
- 5 PAUL, J. R., and BUNNELL, W. W. The presence of heterophile antibodies in infectious mononucleosis, *Am Jr Med Sci*, 1932, clxxiii, 90-104.
- 6 DAVIDSOHN, I. Serologic diagnosis of infectious mononucleosis, *Jr Am Med Assoc*, 1937, cviii, 289-294. Test for infectious mononucleosis, *Am Jr Clin Path*, 1938, viii, 56-60.
- 7 STUART, C. A., WELCH, H., CUNNINGHAM, J., and BURGESS, A. M. Infectious mononucleosis, *Arch Int Med*, 1936, lxvi, 512-522.
- 8 SOHIER, R., PARNET, J., and BERNIER, G. Diagnostic sérologique de la mononucléose infectieuse par le test d'agglutination (réaction de Paul-Bunnell). Sa valeur pratique, *Bull et mem Soc méd d hôp de Paris*, 1939, lv, 846-854.
- 9 WARREN, E. W. Observations on infectious mononucleosis, *Am Jr Med Sci*, 1941, lci, 483-489.
- 10 BEPP, P. The heterophile antibodies in infectious mononucleosis and after the injection of serum. *Ir Clin Invest*, 1936, xv, 591-599.

- 11 FISCHER, Q Bewertung der Agglutination von Hammelblutkoerperchen durch menschliches Serum bei Komplementbindungsreaktionen, Ztschr f Immunitatsforsch, 1931, LVIII, 154-158
- 12 DE VRIES, S I The icteric form of glandular fever, Act med Scand, 1938, CV, 552-565
- 13 BRNSTEIN, A Infectious mononucleosis, Medicine, 1940, XIX, 85-159
- 14 BAILLY, G H Respiratory immunity in rabbits III The production of heterophile antibody in rabbits by intranasal infection with *Bacterium leprosepticum*, Am Jr Hyg, 1928, VIII, 398-409
- 15 BAILEY, G H, and SHORR, M S Heterophile antigen in pneumococci, Am Jr Hyg, 1931, XII, 831-856
- 16 HEDLN, K Ueber das Vorkommen von heterogenetischen Antikoepern (F-Antikoepern) bei der Gonorrhoe, ueber F-Antigen bei Gonokokken, und ueber die aktivierende Einwirkung der Gonokokken auf F-Hapten, Acta dermat-venereol, 1938, XIX, 263-315
- 17 SHORR, M S, and BAILLY, G H Heterophile antigen in various bacterial species, Am Jr Hyg, 1934, XL, 148-183
- 18 SCHULZ, F Flocculation of alcoholic red cell extracts by different types of human heterogenetic hemagglutinins, Jr Immunol, 1937, XLXIII, 315-321
- 19 KOHN-SPEYER, A C Comparative lability of antisera cytotoxic to cancer cells, Lancet, 1927, II, 377-378
- 20 DAVIDSON, I Isoagglutinin titers in serum disease, in leukemias, in infectious mononucleosis, and after blood transfusions, Am Jr Clin Path, 1938, VIII, 179-196

THE TREATMENT OF DELIRIUM TREMENS WITH FARADIC SHOCK THERAPY; A NEW APPROACH BASED UPON THE PSYCHOBIOLOGICAL CONCEPT*

By NATHANIEL J BERKWITZ, M D , P H D , *Minneapolis, Minnesota*

DELIRIUM tremens is an acute alcoholic psychosis which usually follows a prolonged debauch, but which may also appear as an episode in the course of chronic alcoholism. It occurs in less than 10 per cent of all alcoholic admissions¹. It is characterized by illusions, terrifying hallucinations, marked tremors and profuse perspiration. Usually it is preceded for several days by anorexia, restlessness and fear, but it may come on acutely. Kraepelin² stated that its duration varied from a few days to two weeks, but recent workers report that the average case recovers in four to six days³. Besides the typical cases, some run a shorter course (abortive cases) and some go into a subacute or chronic condition (Korsakoff's psychosis or "chronic alcoholic delirium"). The mortality in uncomplicated cases of delirium tremens is about 4 per cent, but it is as high as 25 to 40 per cent when the cases are untreated or when the delirium occurs in association with pneumonia or other infection.

There is no general agreement about the underlying mechanism of delirium tremens. Some believe that the mental symptoms are due to toxic changes in the cortical and ganglionic cells,⁴ or to cerebral edema ("wet brain")⁵. But most recent investigators claim that the histological changes in the brain are obscure in uncomplicated cases, and that the changes found do not differ from those seen in chronic alcoholism without delirium⁶. Also, the "wet-brain" theory now has fewer supporters. Results obtained with dehydration and spinal drainage have not been superior to those obtained with rehydration⁷. A few writers⁸ still maintain that abstinence from alcohol is the chief causative factor of delirium tremens, but the majority of writers recommend abrupt withdrawal. Bowman, Wortis and Keiser⁹ point out that the marked aversion toward food and alcohol in the prodromal period is due to acute gastritis and hepatitis and that abstinence is a result rather than the cause of the delirium. Since anorexia is so common in the prodromal stages, many now regard a sudden deficiency in vitamin intake as the cause. Keme, Streitweiser and Miller¹⁰ urge the use of vitamin B₁, claiming that neither the toxic effects of alcohol nor its sudden withdrawal bring on delirium tremens.

Several workers¹¹ have recently reported that they were able to shorten the duration of delirium tremens with insulin and metrazol shock treatment.

* Received for publication March 24, 1941.

From the Division of Nervous and Mental Diseases, University of Minnesota, and the Neuropsychiatric Division of the Minneapolis General Hospital.

Steck¹² and Robinson¹³ report that they have been able to shorten the duration of the delirium to an average of 2.5 days with insulin sub-shock therapy. Robinson believes that "toxic intermediate products due to deficient carbohydrate metabolism and deficient liver function produce the pathology and symptoms of delirium tremens and that the administration of insulin reestablishes normal carbohydrate metabolism." At the Bellevue Hospital, Orenstein et al¹⁴ report that they have shortened the duration with sub-convulsive doses of metrazol. They ascribe their results to direct stimulation of the central nervous system by the action of the metrazol.

Although many writers have suggested that psychogenic factors have an important bearing on delirium tremens, this important phase has been relatively unexplored. Jewett¹⁵ believes that delirium occurs especially in those who are liable to mental and sensory hyperesthesia. Strecker and Ebaugh¹⁶ point out that shadows in darkness increase fears and disorientation which accounts for patients being more disturbed at night. Bowman et al⁹ stress the need of considering the psychogenic factors, since fear is usually the primary effect of this condition. According to Fantus¹⁷ the development of delirium "depends on (a) the severity of the toxemia or malnutrition, and (b) the constitutional and emotional stability of the patient at the time of illness," and that "patients under emotional tension may develop delirium from relatively slight causes."

Any acute toxic disturbance primarily affects the sensorium-intellect which in turn affects judgment, orientation and emotion. The resulting symptom-complex is known as delirium. This symptom-complex closely resembles the delirium which results from psychogenic disturbances. The emotional tone of delirium is usually that of anxiety, apprehension, or terror. Since most chronic alcoholics are constitutionally inferior or emotionally unstable, it is evident why delirium so often occurs in cases of severe intoxication. Since acute and unpleasant psychotic symptoms in the psychogenic psychoses are often terminated rapidly with shock treatment, the writer has sought to determine whether or not the duration of the psychoses which occur with alcoholism could also be shortened by the same method of treatment. The faradic shock treatments were administered in conjunction with the usual routine medical treatment.

Seventy-six patients under 55 years of age, diagnosed as having uncomplicated conditions of delirium tremens, were included in this study. These were selected from a total of 274 patients admitted for various forms of alcoholism on the Neuropsychiatric Service of the Minneapolis General Hospital. This unusually high proportion of delirium tremens admissions can be attributed to the large number of impending delirium tremens cases transferred from the city jail and the workhouse. Patients over 55 years of age were not considered in this study, in order to exclude the cases which might have irreversible brain damage from cerebral arteriosclerosis or advanced chronic alcoholism.

METHOD OF TREATMENT

The routine medical treatment for all alcoholics with psychoses was as follows (1) prompt withdrawal of alcohol, (2) 100 cc of 50 per cent glucose solution intravenously with 15 units of regular insulin in the more severe cases, (3) paraldehyde, chloral hydrate or other rapidly acting strong sedatives when necessary, (4) physical restraints when necessary, (5) fluids forced and 10 grains of sodium chloride t i d , (6) 10 grains of brewers' yeast t i d , and 1 cc of cevitamic acid, subcutaneously, each day, (7) a high carbohydrate diet, and (8) an ounce of magnesium sulfate the first morning in the hospital. As in most charity hospitals, ideal treatment was not always practicable for financial reasons. Because of limited nursing help delirious patients were often placed in restraints. Strong sedation was not prescribed during the day unless the patient was extremely restless or disturbing to others. For the purpose of comparison in the present study the duration of the delirium was measured by the number of days strong sedation was required for restlessness and sleep.

Only a brief description of the apparatus and technic used in administering faradic shock therapy is given here, for a detailed account of these was presented in a previous paper¹⁸. One electrocardiograph electrode was applied to the forehead and another to the back of the neck. A series of 15 subconvulsive electrical shocks was given with a faradic current of one-half second's duration at intervals of one-half second. This current was produced by an induction coil energized by a six-volt dry cell battery, type A. The patient received an average current of about 10 milliamperes in each shock. A sinusoidal current may be used in place of the faradic current, but a higher amperage would then be required. Immediately following the series of electrical shocks an intravenous injection of pentothal sodium was given. Eight to 10 cc of a 5 per cent solution were required to produce general anesthesia for three to five minutes in chronic alcoholic patients. In a few cases sleep was not produced even with this large amount, but larger dosages were not given. Upon awakening, the patient was usually confused and poorly coordinated for only a few minutes. As the effects of the pentothal sodium wore off, the patient's apprehensiveness, hallucinations, and tremors diminished or left entirely. His intellectual faculties cleared and he remained in a relaxed condition. He was then in a more receptive state to receive reassurance and explanation of the cause of his mental disturbances. Two patients became more disturbed when given an insufficient amount of pentothal sodium solution (less than 6 cc) to produce relaxation. In these two cases, after more pentothal sodium was injected, complete relaxation followed. These shock treatments were repeated daily until all apparent symptoms of delirium disappeared. Some of the patients resisted the administration of the treatment, but after it was given they were grateful for the relief obtained and submitted more readily to following treatments if more were required. After each treatment the pa-

tient was not permitted to remain in bed, but was taken into the day room, encouraged to mix with other patients and to take an active part in occupational therapy. This procedure is considered an essential part of the treatment.

Many of the patients treated with faradic shock therapy did not receive their first treatment for two or more days after their admission to the hospital because of questionable diagnoses. The various types of acute alcoholic psychoses (pathologic drunkenness, abortive forms of delirium tremens, and delirium tremens), at their onset often do not lend themselves to precise clinical differentiation. If the condition in these doubtful cases became aggravated, and if it were permissible, faradic shock treatment was given.

CASE REPORTS

Case 10 J. S., a male, aged 35 and single, had been emotionally unstable since childhood. His father and three brothers were heavy drinkers. The patient began to drink at 16 years of age. He had never been able to hold a steady job. He had been arrested 12 times for alcoholism and had had delirium tremens at least seven times. After his most recent arrest, he had been transferred to the hospital because he had become markedly disturbed at the city jail. As soon as he entered the hospital he begged for paraldehyde. He was seeing giraffes, monkeys, and lilliputians. He was given 3 drams of paraldehyde and 50 c.c. of 50 per cent glucose intravenously with 15 units of insulin. It was necessary to repeat the paraldehyde during the night. Because of his delirious and destructive behavior he was kept in restraint almost constantly, and was given 3 drams of paraldehyde three to four times daily, for four days. Since he did not show improvement, but continued to be restless and disturbed, on the fifth day he was given a faradic shock treatment with 10 c.c. of pentothal sodium, intravenously. Following this treatment his hallucinations disappeared and he remained quiet for three hours. Again he began to beg for paraldehyde. He became so disturbing to the other patients that he was given paraldehyde several times that afternoon and night. As the following day was Sunday, he did not receive shock treatment but he required paraldehyde three times that day. On Monday, the seventh day in the hospital, he was given the second shock treatment. From then on he required no further sedation during the day. He continued to improve after the second and third treatments, and was given chloral hydrate only at bedtime. After the fourth treatment he was no longer apprehensive or restless and he required no further sedation. Because he was such a difficult problem he was given a fifth treatment to insure against possible relapse.

Case 12 K. T., a male, aged 39, married three times, a college graduate and a successful business man, had been a periodic drinker for many years. In the year preceding admission he had had three attacks of delirium tremens. Each attack lasted three to four days. Prior to the present attack he drank from one to two quarts of whiskey daily for over a week. He then began to see animate objects on the wall and undertakers in his room. Because of his noisy and disturbed condition, the police were called and he was taken to the General Hospital late at night. He was placed in restraint, and given 2 drams of paraldehyde and 15 grains of chloral hydrate. Early in the morning he again became disturbed, and the same medication was repeated. Later that morning he was given a faradic shock treatment with 8 c.c. of pentothal sodium intravenously. After the treatment he showed marked improvement. He was discharged that same evening, since he appeared to be fully recovered and insisted on being discharged. When seen five months later, he vouched that he had not touched liquor since he left the hospital.

Case 17 C B, a male, aged 40, and married, had been a heavy drinker since the age of 18. For many years his wife had threatened to divorce him because of his excessive drinking. Prior to admission, he drank from one pint to one quart of whiskey daily for six months. When he could not get whiskey he drank denatured alcohol or bay rum. Because of frequent intoxication he lost his job as a common laborer with the WPA. Shortly after this he was brought to the hospital in a delirious condition. He was placed in restraint and was given paraldehyde several times that night and the following day. The second morning he was given a faradic shock treatment with 10 c c of pentothal sodium each day for four days. After the first two treatments he was given chloral hydrate only at bedtime. He no longer had visual and auditory hallucinations after the second treatment. He remarked "That treatment surely clears my head in a hurry—it is much better than that paraldehyde." He appeared to be fully recovered after the third treatment, but was given one additional treatment.

One month after his discharge he was still unemployed. He returned to the outpatient department for a nerve sedative. Two months later he became depressed because he could not obtain work. He again began to drink heavily. Four weeks later he again became delirious and was readmitted to the hospital. He was given 50 c c of 50 per cent glucose intravenously with 15 units of insulin and one-quarter grain of morphine sulphate. After two hours of sleep he became so disturbed and noisy that he was given 2 drams of paraldehyde and 15 grains of chloral hydrate and placed in restraint. The following day he refused faradic shock therapy because he was apprehensive and afraid to take it. Because of his attitude, sedation was purposely withheld that day. He continued to be so extremely restless and disturbed that 3 drams of paraldehyde were required every four hours on the third and fourth days. His hallucinations and delusions persisted. He saw strange animals and believed that some men wanted to kill him. On the fifth day, after being told that he could have no more paraldehyde, he consented to receive faradic shock treatments. After the first treatment his hallucinations disappeared. He confessed that he should have taken the treatment when it was first offered for it helped him greatly. After the second treatment he remarked "Don't give me any more paraldehyde—it only makes me more dopey and confused." He became cooperative, sociable, neat in appearance, and slept without sedation. After the third treatment he was symptom free.

Case 19 G K, a male, aged 43 and single, had been an alcoholic for 23 years. He was admitted to the hospital on September 1, 1940, in his third attack of delirium tremens within two years. He frequently begged for paraldehyde, but refused the faradic shock treatment. Because of his violent and disturbing behavior he was given paraldehyde every day during his 10 day stay in the hospital. Four months later, following another debauch, he was readmitted in a delirious state with marked tremors, profuse perspiration and terrifying hallucinations. He was given 3 drams of paraldehyde on the night of admission and five times the following day. His condition grew worse. On the second morning he was given a faradic shock treatment with 8 c c of pentothal sodium. His hallucinations disappeared after the shock treatment. After his noon meal he remarked that it was the first good meal he had had in a week. Toward evening he again became restless, continuously paced the floor, but the hallucinations did not return. At night he was given 3 drams of paraldehyde for sleep. The following morning, after the second faradic shock treatment, all his symptoms disappeared and he required no further sedation. He was kept in the hospital five more days for further observation and to provide him with another fresh start.

Case 26 K H., a male, aged 31, single, a meat cutter, had been a heavy drinker since the age of 17. After an alcoholic debauch of six weeks' duration he stopped drinking abruptly so that he could return to work. Three days later he began to see

lions, prairie chickens, and other animals. He became so frightened and excited that the police were called at an early hour to take him to the hospital. He was given 3 drams of paraldehyde, but he again became markedly disturbed three hours later. His excitement continued until he was given a faradic shock treatment with 10 c.c. of pentothal sodium. Following this treatment he remained calm, his hallucinations left, and he required no further sedation. The second morning he was quiet and rational, but slightly tremulous. After the second faradic shock treatment he showed no further symptoms.

Case 28 J F, a male, aged 42 and married, had been committed for alcoholic psychosis to the St. Cloud Veterans' Hospital on three previous occasions. For three weeks before his admission to the Minneapolis General Hospital he drank one quart of whiskey every day and took two to three ounces of paraldehyde every night for sleep. Three days before his admission he stopped drinking abruptly. He was taken to the hospital in a delirious condition. He was given 3 drams of paraldehyde that night and three times the following day. As this failed to quiet him, he begged for more. The second morning he was given a faradic shock treatment with 10 c.c. of pentothal sodium. Greatly improved after the treatment, he said "Yesterday I would have drank anything that I could lay my hands on, but now I swear I will never drink again." No further sedation or shock treatment was necessary because he showed no further symptoms. He was kept in the hospital, however, three more days for further observation.

Case 30 D F, a male, aged 37, single, a garage mechanic, had been a periodic drinker since the age of 20. After drinking heavily for 10 days, he was taken to a private hospital in a disturbed condition. He was transferred to the Minneapolis General Hospital the following evening because he became so belligerent and violent. He thought men were threatening him with knives and saw some staring at him from the ceiling. He refused paraldehyde that evening because of nausea and remained extremely restless throughout the night. The following morning, after receiving a faradic shock treatment with 10 c.c. of pentothal sodium, he showed much improvement. In the afternoon his hallucinations returned, and he again became noisy. That evening he was given paraldehyde and chloral hydrate twice. The following morning, after the second faradic shock treatment, he showed no further symptoms. He told the nurses and other patients how much the shock treatment had helped him. He was kept in the hospital two more days for observation.

Case 31 A T, a male, aged 36, single, and a bartender, drank heavily periodically for 18 years. He had had delirium tremens one year previously. He drank more than one quart of whiskey daily for six weeks until five days before admission to the hospital. Visual hallucinations appeared one day before his admission. On admission he was tremulous, fearful and excited. He slept very little that night, although on two occasions he received 2 grains of phenobarbital and $\frac{1}{400}$ grain of hyoscine hydrobromide subcutaneously. The following morning he was seen picking imaginary spiders off his blanket. He also complained that a little negress was throwing lice at him. Although oriented as to time and place, he saw scores of penguins as large as sheep. He was given a faradic shock treatment with 10 c.c. of pentothal sodium. Two hours after the treatment he was not so restless, but he was again confused. When asked where the penguins were he hunted about the room, remarking "That is strange. I saw them here before." In the afternoon, although he was less disturbed, he again saw the penguins but they were smaller in size. Some were small enough to crawl through cracks. Later in the same afternoon after a second treatment, he again improved. He played checkers and was greatly pleased with the relief the treatment gave him. In the evening, however, he again became restless and tremulous. He was given 2 grains of sodium luminal intravenously and $\frac{1}{400}$ grain of hyoscine subcutaneously for sleep. The following morn-

ing, after the third faradic shock treatment, he fully recovered. Later in the day he remarked "I really thought that I saw penguins yesterday. I must have been insane. I sure feel fine now." The change in his behavior and attitude was remarkable. He was not discharged until two days later, however, so that he could be provided with a fresh start.

SUMMARY OF RESULTS

Since the use of faradic shock therapy in the treatment of delirium tremens was considered as an experimental procedure, the hospital regulations did not permit us to force its use on unwilling patients. Written consent was frequently denied to us because the nature of such a request seemed to imply to many that the treatment entailed certain dangers. Consequently, we were unable to treat every other admission of delirium tremens with this treatment*. As stated above, all patients, whether given shock treatment or not, received the same routine medical treatment. The group which received faradic shock therapy (table 1) includes those who gave consent and those who were in no condition to give consent and whose relatives could not be reached. The group not treated with faradic shock therapy (table 2) includes those who strongly objected to the shock treatment and those who, on admission, had such mild symptoms that they were at first regarded as having abortive forms but later were considered as milder forms of delirium tremens, since their symptoms did not abate promptly with the usual routine medical treatment. It is obvious, therefore, that most of the severe cases were among the first group.

Thirty-three cases of delirium tremens in Group I were given faradic shock therapy in addition to the routine medical treatment, and 43 were given only the routine medical treatment (Group II).

Among the 76 patients reported in this paper there was only one death. This patient did not receive faradic shock treatments. He showed no evi-

* Beginning January 1, 1941, the writer obtained permission from the Minneapolis General Hospital administration to administer faradic shock therapy to patients with delirium tremens without obtaining their written consent. A better controlled statistical evaluation was thereby made possible. To determine the relative effectiveness of paraldehyde, intravenous barbiturates, and faradic shock therapy with intravenous pentothal sodium, all uncomplicated cases under 55 years of age on admission were assigned in alternation to three groups. The interns were instructed to prescribe strong sedation to all patients in the three groups only when it was urgently required. Whenever intravenous medication failed to quiet the patients in the second and third groups, 3 drams of paraldehyde were given one-half hour later. Thirty patients were admitted from January 1 to July 1, 1941, so in each group there were 10 patients. The 10 patients in the first group who received paraldehyde recovered in an average of 37 days, the 10 patients who received intravenous barbiturates (pentothal sodium or sodium amytal) in 27 days, and the 10 patients who received faradic shock with intravenous pentothal sodium in only 19 days. The writer believes that the results in the first group were lower than the average of 50 days reported in this paper because the paraldehyde was withheld more stringently. The second group responded still more promptly, indicating that intravenous barbiturates further shorten the duration of the delirium. In the third group the duration was shortened from the average of 22 days reported in this paper because in all cases the faradic shock treatment was administered on the first morning of admission. These results indicate that intravenous barbiturates shorten the duration of delirium tremens but when used in conjunction with faradic shock treatment the duration of the delirium is further shortened.

dence of infection until 36 hours after admission, when his temperature began to rise. He expired from pneumonia shortly afterwards.

In only one case was a patient treated twice on the same day with faradic shock. There is no reason why this treatment should not be given twice daily if the patient shows need for it. This may further shorten the duration of the illness.

TABLE I

Group 1, Delirium Tremens Treated with Faradic Shock Therapy

Case No. and Name	Sex	Age	Days in Hospital Before Faradic Shocks Given	Days Faradic Shocks Given	Days Strong Sedation Required After 1st Treatment	Days Strong Sedation Required in Hospital
1 NN	M	33	1	2	1	2
2 PH	M	39	1	5	4	5
3 FH	M	39	2	1	0	2
4 SB	M	39	2	2	0	2
5 NH	M	35	2	2	1	3
6 RF	M	34	1	1	0	1
7 ES	M	43	2	2	0	2
8 EC	M	38	1	1	0	1
9 GB	M	48	1	1	0	1
10 JS*	M	35	4	5	4	8
11 TT	M	47	3	2	1	4
12 KT*	M	39	1	1	0	1
13 RH	M	36	2	2	0	2
14 PH	M	39	2	2	2	4
15 GJ	M	40	1	2	0	1
16 EB	F	39	2	1	0	2
17 CB*	M	40	2	4	0	2
†			5	3	1	6
18 PM	M	41	1	1	0	1
19 GK*	M	43	1	2	1	2
20 SE	M	34	1	1	0	1
21 TT	M	47	1	2	0	1
22 TF	M	34	1	3	0	1
23 FC	F	40	2	6	3	5
24 ST	M	46	1	3	0	1
25 DL	F	41	1	1	0	1
26 KH*	M	31	1	2	0	1
27 LL	F	40	2	1	0	2
28 JF*	M	42	1	1	0	1
29 AD	F	48	1	2	0	1
30 DF*	M	37	1	2	1	2
31 AT*	M	36	1	2	1	2
32 CB	M	44	3	3	0	3
33 EB	M	43	1	2	0	1

* See case report

† Second admission

There was very little difference in the ages of the two groups. The average age in Group I was 38.5 years, and in Group II it was 40.5 years.

The average number of daily shock treatments administered was 2.2. A few patients received an extra treatment after all symptoms disappeared to make certain that recovery was complete.

The mean number of days strong sedation was required in Group I was 2.21 with a standard deviation of 1.66, as compared with the mean of 5.05

days with a standard deviation of 3.33 in Group II. The difference of the means was 2.84 ± 0.59 . The ratio of the difference to the standard error of the difference was 4.82. Therefore, the probability of the difference arising through chance alone would be extremely small.

The average number of days before administration of the faradic shock therapy was 1.6, for several did not receive this treatment for two or more days after their hospital admission. It is quite probable that the duration of the delirium could have been shortened if all the patients in Group I had been given their first treatment on admission.

TABLE II
Group 2, Delirium Tremens Treated without Faradic Shock Therapy

Case No. and Name	Sex	Age	Days Strong Sedation Required in Hospital	Case No. and Name	Sex	Age	Days Strong Sedation Required in Hospital
1 H L	M	39	4	23 S T	M	45	6
2 G M	M	27	2	24 J L	M	35	10
3 M B	M	43	5	25 P C	M	38	4
4 M M	M	33	13	26 H L	M	39	5
5 L H	M	49	3	27 B J	M	42	4
6 C B	M	45	10	28 T F	M	35	5
7 E S	M	50	5	29 S H	M	38	9
8 J C	M	35	5	30 E B	F	39	9
9 A K	M	49	3	31 G B	M	41	3
10 D E	M	39	3	32 D H	M	42	4
11 L H	M	50	5	33 G H	F	34	4
12 A B	M	46	4	34 B S	F	34	2
13 M W	F	32	4	35 S B	M	42	19
14 E O	F	29	4	36 E S	M	41	2 (died)
15 H L	M	39	4	37 P F	M	45	3
16 G A	M	46	2	38 R A	M	32	2
17 S B	M	42	3	39 C B	M	42	4
18 D S	F	35	3	40 B P	M	49	7
19 L J	M	32	3	41 G D	M	47	3
20 W C	F	31	3	42 J C	M	36	2
21 G K	M	43	10	43 E Y	F	46	6
22 J C	M	35	6				

The average number of days strong sedation was needed after the first faradic shock treatment was only 0.6 days. This low figure strongly indicates the effectiveness of the treatment. Only six, or 17 per cent of the 33 patients, of those treated with faradic shock reached or exceeded the median number of days strong sedation was required in those who received only the routine medical treatment.*

* Four cases of pathologic drunkenness recovered promptly after they were given one faradic shock treatment. Two cases of Korsakoff's psychoses were also treated with faradic shock treatment. They developed delirium, extensive confabulation and peripheral neuritis after several months of heavy drinking. The symptoms of delirium disappeared after two faradic shock treatments, but they continued to be mildly confused at night for several days. The peripheral neuritis, however, persisted for several months. In addition to these cases, other forms of toxic psychoses treated with faradic shock treatment will be discussed in a future report.

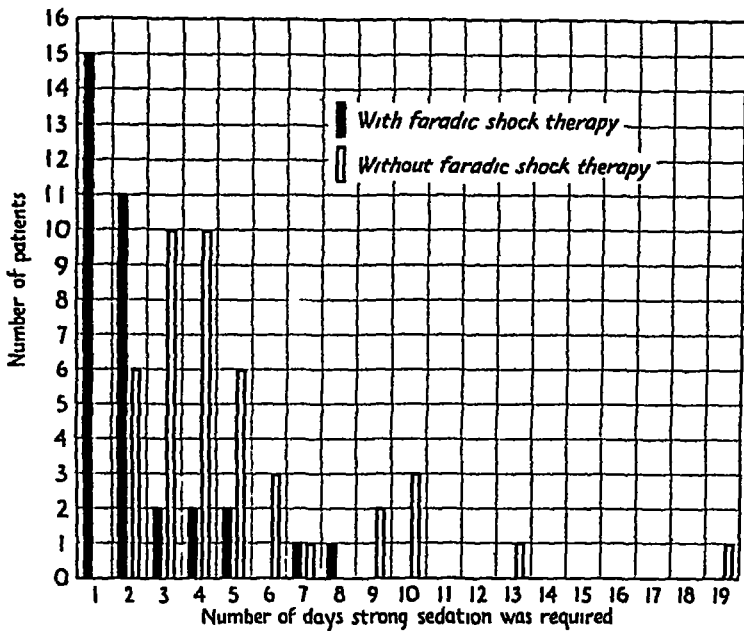


FIG 1 Graphic representation showing the number of days strong sedation was required by patients with the symptom-complex of delirium tremens. Forty-three cases were treated with routine medical treatment (white bars), and 33 cases were treated with the same routine treatment together with faradic shock therapy (black bars)

COMMENT

As early as the first half of the nineteenth century, Esquirol¹⁹ considered alcoholism as a symptom rather than a cause of the psychosis. Janet²⁰ commented that the "patients themselves have not been alcoholics all their lives, but they were already sick persons before they took to drink." In a searching study of 65 cases he found that over 50 of these exhibited multiform neuropathic symptoms before they took to drink. In a recent study of 97 cases Davidoff and Whitaker²¹ corroborated his observations. Alcohol furnishes the easiest means of escape from disagreeable reality, for it temporarily blurs or obliterates unpleasant situations. Unfortunately, however, in many cases habituation ultimately follows.

Besides the psychogenic factors, several physiologic conditions also contribute to the etiology of delirium tremens. Many in the past considered sudden withdrawal of alcohol the cause, but now only a few consider it an important factor. In all forms of drug addiction, the physiologic processes of the organism gradually become accustomed to the drug. Therefore, a sudden abstinence produces a temporary dysfunction of the autonomic nervous system. The resulting physiologic disturbances are responsible in part for such symptoms as restlessness, apprehensiveness and anxiety. Hence, a sudden withdrawal must be considered as an important contributory factor in the production of delirium.

Another contributory factor is malnutrition. This condition often occurs in the course of a prolonged drinking bout. Since the rôle of vitamins has recently come to the foreground, some workers now maintain that avi-

taminoses are the cause of the delirium. Although subvitaminoses may often occur, there is, as yet, no conclusive evidence that vitamin deficiency alone causes delirium tremens. In a recent study by Rosenbaum et al,²² it was found that once the disorder starts, vitamin therapy does not seem to shorten the illness. Nevertheless, all patients in this study were treated for malnutrition.

Since all traces of alcohol leave the body in less than 24 hours, some hold that delirium tremens is not caused by the toxic effects of the drugs alone. It is well known, however, that alcoholic intoxication impairs judgment and orientation by the involvement of the higher centers (sensorium-intellect). These changes secondarily affect the emotions-will field and the autonomic nervous system which creates emotional excitement and fear. As early as 1886, Blandford²³ stated that "the toxic effects of alcohol reduce the nerve centers to such an unstable state that the slightest thing such as an accident, grief, anxiety or mental shock upsets the balance." Today these same conditions are recognized as precipitating factors in psychogenic psychoses, or in delirium tremens, or following a prolonged drinking bout.

Therefore, delirium tremens is not an isolated organic disorder, but rather a symptom-complex resulting from psychogenic as well as physical causes. Mental disturbances arising from psychogenic or physical causes show themselves chiefly through alterations of physiologic functions (autonomic nervous system dysfunction). Objective symptoms such as perspiration, anorexia, tremors, and vasomotor reaction which occur in delirium, arise from difficult life-situations, toxic-organic processes, or both. Thus, it is necessary to regard the human organism as an integrated unit. Fortunately, this concept is gradually replacing the dualistic view that mind and body are separate entities. It is bringing about a better understanding of how disturbances of the personality may result from psychologic or toxic-organic causes or both (figure 2). With this consideration the treatment of delirium tremens may be carried out more effectively.

SUMMARY

Although there is no specific treatment for chronic alcoholism, the symptom-complex of delirium tremens is curable. In Osler's textbook²⁴ appeared a statement "Delirium tremens is a disease which, in a large majority of cases, runs a course very slightly influenced by medicine." Although many may still hold this belief, observations of the recent investigators do not support this view. A conspicuous difference occurs in the mortality rates in the places where the cases are poorly treated and where adequate supportive and protective therapy is provided.

Although sudden withdrawal of alcohol often produces dysfunction of the physiologic processes in individuals whose organism has become habituated to the drug, the writer concurs with the majority in advocating this method of treatment. Practically all chronic alcoholics intend to "taper off" of their own accord, but they usually fail. It is poor medical practice

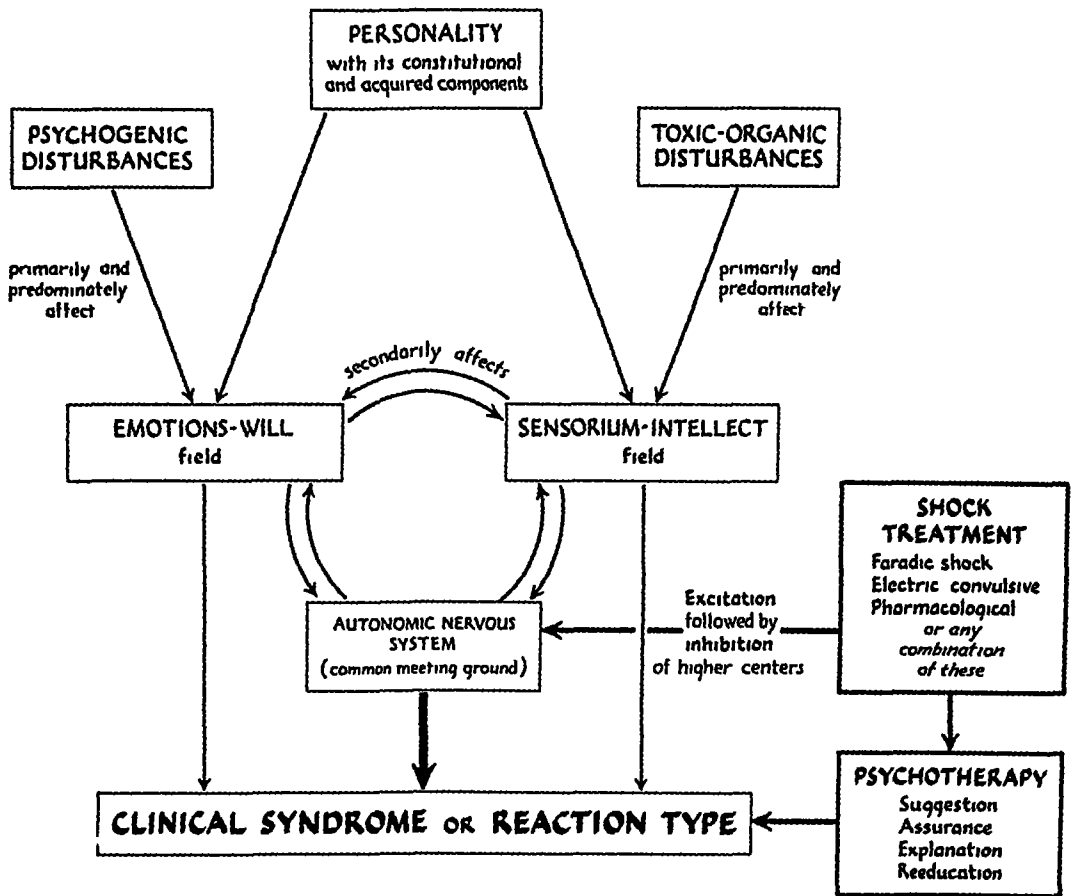


FIG 2 Scheme showing how psychogenic or toxic-organic disturbance may affect the physiological processes and produce similar symptoms. If the psychogenic disturbances are not systematized and if the toxic-organic changes are not irreversible shock treatment used in conjunction with psychotherapy may remove the psychotic symptoms by breaking the vicious circle.

for a physician to prescribe gradual withdrawal because it gives the patient professional sanction to a procedure which is fraught with danger. The patient and his relatives are led to believe that such a procedure is necessary and proper. Gradual withdrawal frequently prolongs and at times aggravates the condition.

Supportive and protective measures are essential in the treatment of delirium tremens. The various supportive measures necessary to maintain the vital functions and support the strength of the patient have been already described. The procedures used in this study are similar to those employed at the Bellevue Hospital²⁵ and at other leading centers.

The protective measures, chiefly physical and chemical restraints, were used to avoid accidental injuries and to prevent exhaustion. Paradoxical as it may sound, these measures, although essential, often prolong or aggravate the condition. Particularly at night, it was often necessary to use physical restraints for violent and disturbed patients, even though such methods often provoke constant struggle which causes further excitement and exhaustion. Since the action of sedative drugs on these patients is uncer-

tain, the application of restraints as a safeguard was often necessary, for without them constant vigilance would be required, but this is not practical in a general hospital because of the expense involved. Individual nursing care would be ideal, for the application of restraints would not be so often required. Continuous tub baths are far superior to the use of physical restraints, but as in most other general hospitals such equipment was not available. Sedative packs were not used for they also tend to increase the excitement by the restraint involved.

The use of chemical restraints presents as difficult a problem as that of physical restraints for they also are easily subject to abuse. The most satisfactory sedative used to produce sleep and prevent exhaustion in delirious patients is a quickly acting and rapidly eliminated drug. Since these patients often remain wide awake, in spite of heroic administration of hypnotics, it is evident that slowly eliminated drugs which accumulate in the system are contraindicated, for their toxic action may prolong and aggravate the condition.²⁶ According to Jewett,¹⁵ the mortality was reduced more than half when he abandoned their use. Paraldehyde, the most popular drug used in the treatment of delirium tremens, was used most frequently by us. It is not an ideal sedative. Since it is closely related to ethyl alcohol it also irritates the stomach, produces "hangover" effects, induces delirium, and is habit forming. It was not given rectally for it is rarely retained by excited patients. Some advise against the use of paraldehyde for it often increases excitement.²⁷ Intravenous barbiturates are far superior, for their use eliminates most of these undesirable effects. The hypnotic effect is more certain, and the action and elimination are more rapid. Their administration entails no danger if one is fully informed about their pharmacologic characteristics. Several writers²⁸ have claimed good results with intravenous sodium amytal in controlling patients with delirium tremens, but the duration of its action in the excited patients has been so brief that it has not enjoyed a wide use.

In this study intravenous pentothal sodium was used exclusively for sedation following excitation with the series of electrical shocks because it is one of the most rapidly acting and eliminated drugs in the barbiturate series. Since its after effects are very transitory, the patient was in condition to receive psychotherapy soon afterwards.

Since delirium tremens generally has been considered as a purely toxic-organic disturbance, insufficient attention has been given to its psychogenesis. The personality with its constitutional and acquired components must be considered, as well as the various physical factors which contribute to its origin. Although in recent years several writers have pointed out the importance of considering the psychogenic factors, most therapists have continued to treat delirium tremens as a physical disease rather than as a psychobiologic reaction type.

Shock treatment does not change the preëxisting personality of psychotic individuals, but it usually removes unpleasant psychotic material if it is of

rather recent origin.²¹ The same appears to be true in patients with delirium tremens. Shock treatment promptly relieves them of their acute mental symptoms and provides them with a fresh start, but it does not alter their underlying constitutional make-up. It is too early to determine whether faradic shock treatment may defer some from further drinking, but it appears quite likely that by interrupting the vicious circle at the onset acute mental disorders may be prevented from merging into more chronic forms.

Since the symptom-complex of delirium tremens is the result of psychogenic as well as physical conditions, it is logical to conclude that both of these conditions should be treated. By using faradic shock therapy, an apparently safe, effective, and inexpensive method of bringing about a quick relief of acute psychotic symptoms, together with the accepted routine medical treatment, the underlying psychogenic and physical factors are simultaneously treated. The duration of the illness was shortened to less than half the usual time by this procedure. Consequently, the danger of physical complications was also lessened.

CONCLUSIONS

The symptom-complex of delirium tremens results from psychogenic as well as physical conditions. The contributory factors are (a) the personality with its constitutional and acquired components, (b) the toxic effects of alcohol, (c) malnutrition, and (d) sudden withdrawal of alcohol. The precipitating factor may be an emotional shock, injury, or infection.

The routine treatment has been directed largely toward supportive measures, but the basic considerations of the psychopathology have been largely neglected. Experience has shown that the necessary "protective" measures (chemical and physical restraints) often aggravate or prolong the condition. Faradic shock therapy promptly removes the acute psychotic symptoms in most cases and, therefore, lessens the need of these undesirable protective measures.

Seventy-six cases of delirium tremens were given the same routine medical treatment. Forty-three of these, receiving only the routine treatment, required strong sedation for an average of 5.0 days. Thirty-three, receiving faradic shock therapy in addition to the routine treatment, required strong sedation for an average of 2.2 days.

BIBLIOGRAPHY

- 1 MOORE, M., and GRAY, M. G. Delirium tremens: study of cases at Boston City Hospital, 1915-1936, *New England Jr Med*, 1939, ccxx, 953-956.
- 2 KRAEPELIN, E. Clinical psychiatry, Translated by DEFENDORF, A. R., 1902. The Macmillan Company, New York, page 122.
- 3 PIKER, P., and COHN, J. V. The management of delirium tremens, *Jr Am Med Assoc*, 1937, cviii, 345-349.
- 4 GRINKER, R. R. Neurology, 2nd ed, 1937, Charles C. Thomas, Baltimore, page 893.
- 5 SOLLMAN, T. Pharmacology, 5th ed, 1936, W. B. Saunders Company, Philadelphia page 678.

- 6 CLINE, W B, and COLEMAN, J V The treatment of delirium tremens, Jr Am Med Assoc, 1936, cvii, 404-409
- WORTIS, H Delirium tremens, Quart Jr Studies on Alcohol, 1940, 1, 251-267
- 7 THOMAS, J M, SEMRAD, E V, and SCHWAB, R S Observations on the use of fluids and lumbar puncture in the treatment of delirium tremens, ANN INT MED, 1939, xii, 2006-2009
- 8 BRUEL, L Quoted by JELLINEK, E M, and JOLLIFFE, N See reference 11
- 9 BOWMAN, K M, WORTIS, H, and KEISER, S The treatment of delirium tremens, Jr Am Med Assoc, 1939, cxii, 1217-1219
- 10 KEINE, H E, STREITWEISER, R J, and MILLER, H Role of vitamin B₁ in delirium tremens, Jr Am Med Assoc, 1940, cxiv, 2191-2194
- 11 JELLINEK, E M, and JOLLIFFE, N Effects of alcohol on the individual review of the literature of 1939, Quart Jr Studies on Alcohol, 1940, 1, 110-181
- 12 STECK, H Die Behandlung des Delirium Tremens, Schweiz med Wchnschr, 1936, lvi, 68-70
- 13 ROBINSON, G W The treatment of delirium tremens with insulin in sub-shock doses, Am Jr Psychiat, 1940, xcvi, 136-151
- 14 ORENSTEIN, L L, BOWMAN, K M, KAGAN, J R, and GOLDFARB, W Use of metrazol in the treatment of acute alcoholism, Am Jr Psychiat, 1939, xcvi, 589-594
- 15 JEWETT, S P Alcoholism, Practice of Medicine Edited by F Tice, vol 8, 1924, W F Prior Company, Hagerstown, Maryland, page 10
- 16 STRECKLER, E A, and EBAUGH, F G Practical clinical psychiatry, 4th ed, 1935, P Blakiston's Son and Company, Philadelphia, page 214
- 17 FANTUS, B The therapy of acute delirium (toxic psychosis, fever psychosis, manition psychosis), Jr Am Med Assoc, 1940, cxv, 929-933
- 18 BERKWITZ, N J Faradic shock treatment of the "functional" psychosis, Jr Lancet, 1939, lx, 351-355
- BERKWITZ, N J Faradic shock in treatment of functional mental disorders treatment by excitation followed by intravenous use of barbiturates, Arch Neurol and Psychiat, 1940, xlv, 760-775
- 19 ESQUIROL Quoted by JELLINEK, E M, and JOLLIFFE, N See reference 11
- 20 JANET, P Psychological healing, Translated by E Paul and C Paul, vol 2, 1925, The Macmillan Company, New York
- 21 DAVIDOFF, E, and WHITAKER, C A Prepsychotic personality in alcoholic psychoses, Psychiat Quart, 1940, xiv, 103-120
- 22 ROSENBAUM, M, PIKE, P, and LEFEBVRE, H Delirium tremens a study of various methods of treatment Am Jr Med Sci, 1940, cc, 677-688
- 23 BLANDFORD, G F Insanity and its treatment, 1886 William Wood & Company, New York, page 43
- 24 OSIER W, and McCRAE, T The principles and practice of medicine, 1920, D Appleton and Company, New York, page 391
- 25 WORTIS, H Delirium tremens, Quart Jr Studies on Alcohol, 1940, 1, 251-267
- 26 WONDOLOWSKI, L S Aggravation of mental symptoms by excessive use of hypnotics and sedatives, Psychiat Quart, 1940, xiv, 121-127
- 27 HENDERSON, D K, and GILLESPIE, R D Text-Book of psychiatry, 1927 Humphrey Milford, Edinburgh
- 28 BLACKWINS, W I Production of sleep and rest in psychotic cases, Arch Neurol and Psychiat, 1930, xix, 365-372
- ZERIAS, L G Sodium amytal and other derivatives of barbituric acid, Brit Med Jr, 1930, ii 897-902
- PIKE, P and COHEN, I A Comprehensive management of delirium tremens, including treatment utilized in 500 consecutive treatments Jr Am Med Assoc, 1937, cxvii, 345-349
- 29 BERKWITZ, N J Treatment of mental disorders with pharmacological and electrical shock methods, Modest on Med, 1941, xix, 25-30

CARDIO-PERICARDIOPEXY; THE SURGICAL TREATMENT OF CORONARY ARTERIAL DISEASE BY THE ESTABLISHMENT OF ADHESIVE PERICARDITIS *

By SAMUEL ALCOTT THOMPSON, M D , F A C S , and MILTON J RAISBECK, M D , F A C P , *New York, N Y*

CORONARY arterial disease is an ever changing process during the development of which the occlusive process is opposed by the formation of collateral anastomoses. When the adjustments within the heart are sufficient to compensate for the disease process, no symptoms occur, but when a discrepancy exists between the myocardial demand and the coronary supply, the resulting myocardial ischemia is responsible for the clinical syndromes of angina pectoris, congestive failure and myocardial infarction. The coronaries may be completely occluded without infarction or myocardial fibrosis if the development of the collateral circulation keeps pace with the occlusive process. This conception relates particularly to the mechanical effects of the disease, but these effects are the same regardless of the variations in the underlying etiology. The changes in the myocardium depend solely upon the extent and duration of the relative ischemia and not upon the manner in which the ischemia is produced.

The limit of adjustment between blood demand and supply, which has been called the coronary reserve, may be exceeded by an increase in the myocardial demand or a decrease in the coronary supply.

RATIONALE OF SURGERY

The rationale of surgery in the treatment of coronary arterial disease is to decrease the myocardial demand or increase the coronary supply, and has to do with operative procedures upon (1) the sympathetic nervous system, (2) the thyroid gland, and (3) upon the heart itself.

Operations upon the sympathetic nervous system interrupt the cardio-sensory and motor pathways. This prevents the conduction of impulses responsible for painful sensations and possibly for spastic contraction of the coronary arteries. Spasm of the coronary arteries alone may lead to angina or, superadded to disease of an artery, may lead to myocardial infarction.

The operations usually consist in the removal of the upper four or five thoracic and the lower cervical afferent and efferent ganglia, or the nerves of these ganglia. Raney³⁸ reported a series of cases in which he severed only the motor nerves entering these ganglia, on the theory that the presence of

* Received for publication August 1, 1941.

From the Thoracic Surgical Service and the Department of Cardiology of the New York Medical College and Flower-Fifth Avenue Hospitals.

disease reverses the normal physiology and the motor nerves then contract rather than dilate the coronary arteries. The validity of this theory is not established as the operation was performed only upon one side, but because of his reported low mortality and good results, the procedure appears to deserve a further trial. Injection of alcohol into these ganglia and the vertebral nerves, in our experience, has brought only temporary relief. Two of the patients in our series had received injections on two different occasions.

Total removal of the thyroid gland in coronary arterial disease was performed with the idea of reducing the metabolic rate and thereby reducing the myocardial demand to the level of a decreased coronary supply. This has been beneficial in some instances, but in general it has not stood the test of time. For this reason, and because of its high mortality, it is not considered a satisfactory procedure.

Grafting tissue onto the myocardium produces a collateral circulation in two ways: (1) intracardiac, by stimulating an increase in the size and function of the collateral channels which are already present in the heart, and (2) extracardiac, by the formation of new channels from the grafted tissue to the myocardium. This grafted tissue should have, or be capable of producing and maintaining a satisfactory blood supply. This additional blood supply augments the decreased coronary supply, and the myocardial ischemia is overcome not by eliminating coronary arterial spasm and not by decreasing the myocardial demand, but by increasing the actual blood supply to the heart. This comparatively recent principle in the treatment of coronary arterial disease, first applied to a human being by Beck,^{2,3} has been sufficiently demonstrated from experimental and clinical evidence to be physiologically sound. The tissues which have been used as grafts are muscle, omentum, lung and pericardium.

In cardio-myopexy, as developed by Beck, the epicardium is mechanically removed by a burr, and a portion of the pectoralis muscle is partially resected and applied to the denuded myocardium and pericardium. This operation is one of major proportions and must be limited to patients who are in condition to withstand major operative procedures. There is a certain operative mortality in patients with coronary disease, no matter what or how simple the operation.

In cardio-omentopexy, as developed and first performed by O'Shaughnessy,⁴⁻⁷ the left pleural cavity is opened and a portion of omentum is brought up through a small incision in the diaphragm. The pericardium is opened and the epicardium is covered with an irritant salve. The omentum is then attached to the edges of the pericardium. The reaction produced by the salve causes the omentum to become adherent to the myocardium. This operation also is one of major proportions.

Cardio-pneumopexy has been performed upon two patients by O'Shaughnessy without relief of the symptoms.

The ability of the pericardium to serve as the source of a collateral cir-

culatation has been known for some time and as a result of animal experimentation it was definitely recommended for such use in 1932 by Hudson, Moritz and Wearn.² Since that time other investigators have demonstrated the effectiveness of the pericardium as a source from which to develop a collateral circulation. O'Shaughnessy performed the first operation in which the pericardium was used as the source of the collateral circulation. Beck also reported a patient with congestive failure in whom he inserted powdered beef bone into the pericardial sac.

The blood supply of the pericardium is abundant (figure 1). It receives branches from the aorta, from the internal mammary, from the esophageal, from the phrenic, from the bronchial, from the mediastinal, and from the coronary arteries themselves. While these branches are normally small they, nevertheless, constitute a rich source for collateral communication with the coronary arteries.

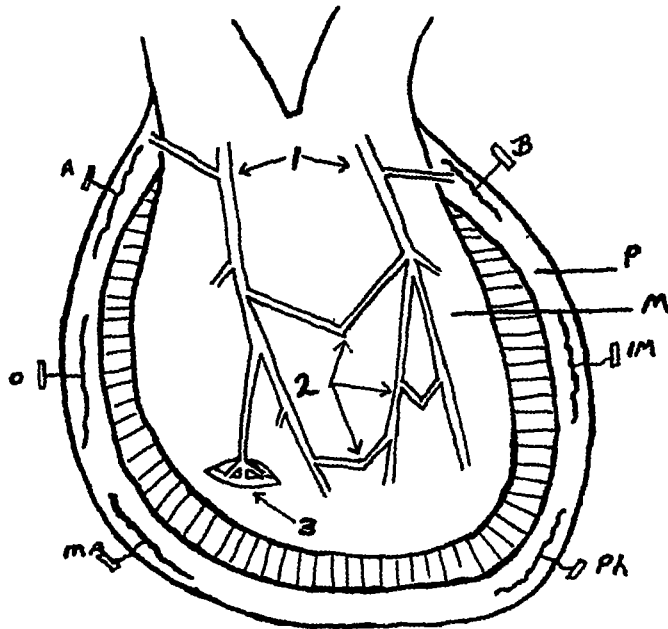


FIG 1 This diagram illustrates the normal coronary artery anastomosis. (1) Extra-cardiac anastomotic branches to the pericardium. (2) Inter-coronary anastomoses between the main coronary arteries. (3) Intra-cardiac anastomoses between branches of the same coronary artery.

The blood supply of the pericardium is also illustrated, the branches received are from the B, bronchial, IM, internal mammary, Ph, phrenic, MA, mediastinal, O, esophageal, A, aortic, P, pericardium, and M, myocardium.

EXPERIMENTAL EVIDENCE

Contrary to the general belief, adhesive pericarditis is not readily or easily produced by mechanical trauma or by a host of chemical irritants. In a series of animal experiments we demonstrated the ability to produce adhesive pericarditis regularly and graft the pericardium on to the epicardium by the introduction of sterile talc powder (hydrous magnesium silicate) into

the pericardial sac* The powder produces a foreign body reaction, characterized by a fibrinous pericarditis, with little or no fluid formation As early as 18 hours after the introduction of the powder the pericardium becomes adherent to the epicardium at the site of insertion After one week the two surfaces are firmly adherent, and after four weeks the pericardium and epicardium are fused as one layer of tissue The presence of blood vessels from the pericardium to the epicardium was demonstrated at subsequent operations when bleeding was observed from both tissues when the two layers were separated Also microscopic sections of injected specimens demonstrate the presence of blood vessels going from one tissue to the other (figures 2 and 2A)

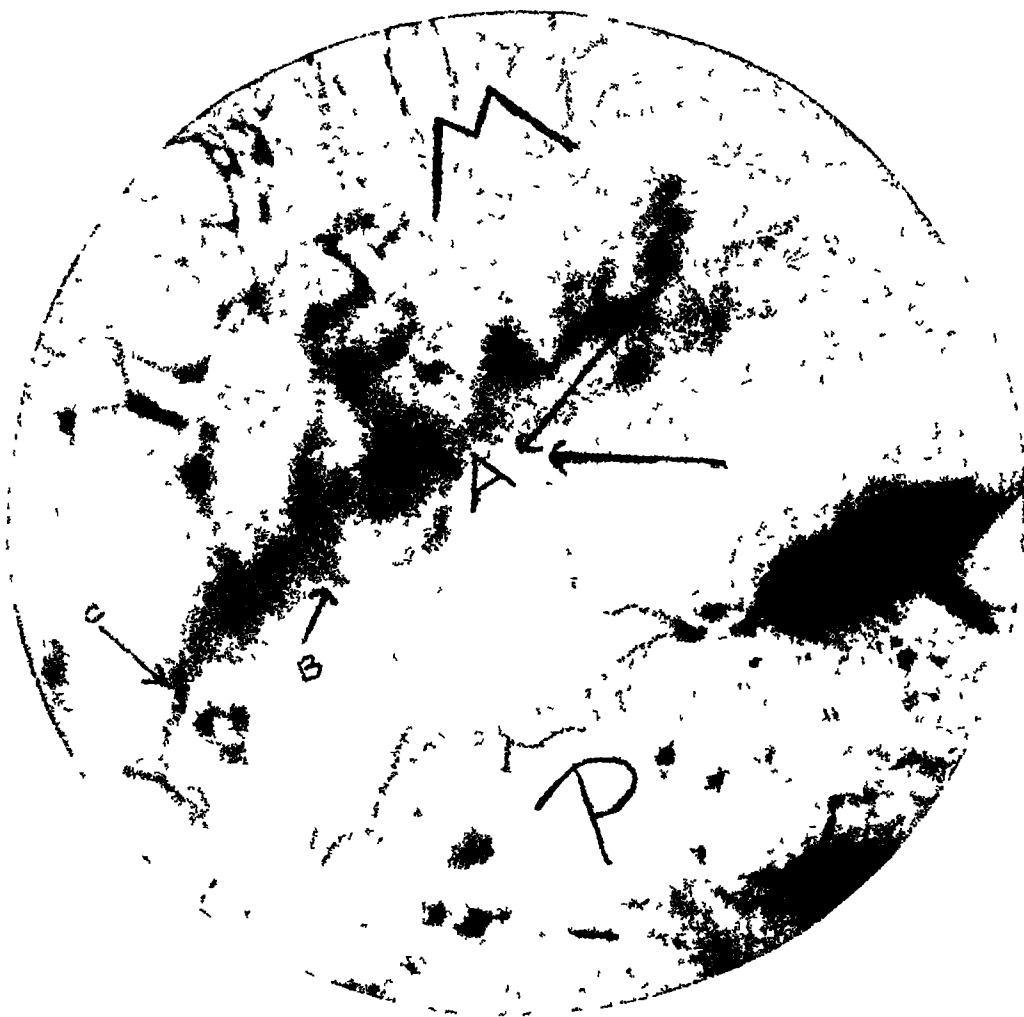


FIG. 2 Photomicrograph (low power) of a section of a dog's heart Adhesive pericarditis was produced and this was followed by ligation of the left descending branch of the coronary artery The dog was later sacrificed and the heart injected with India ink The arrows at A point to the line of cardiopericardial adhesions M, myocardium, P, pericardium At B and C vessels are seen crossing directly between the pericardium and myocardium

* Assistance by Drs. F. A. Furro, Frank Furro, Sidney Green, Melvin Rupp, Alden P. W. Kelly, F. Swager and L. P. Wershub is gratefully acknowledged

Following the introduction of the talc powder a definite inflammatory reaction occurs and involves the pleura, the pericardium, the epicardium and the adjacent myocardium. One of the characteristic features of this reaction is the tremendous hyperemia which is produced within a few hours. The reaction persists for two or three weeks and gradually subsides. We feel that this hyperemia of the myocardium not only opens up the anastomotic channels between the coronaries which are already present, although not in use, but also stimulates the formation of new intercoronary channels. Thus the reaction would be responsible for the formation of new intracardiac as well as extracardiac collaterals.



FIG 2A Photomicrograph (high power) of a section of a dog's heart following cardio-pericardiopexy and ligation of a main coronary artery. The dog was sacrificed and the heart injected with India ink.

The arrows at A point to the line of cardiopericardial adhesions. M, myocardium, P, pericardium. Notice the large vessel filled with ink, crossing directly between the pericardium and myocardium.

Because of the inefficient lymphatic supply of the pericardium and the large size of the powder particle, very little if any of the powder is removed from the pericardial sac. Phagocytosis removes a small amount but the greater part of the powder remains indefinitely in the pericardial sac, fixed in the adherent tissues.

To determine the possibility of applying such a procedure to human beings experiments were done on four groups of dogs. In the first group of 20 dogs the descending branch of the left coronary artery and vein were ligated and divided one centimeter below their junction with the circumflex

branch In this group, which was used as a control, the mortality was 50 per cent In the second group of 16 dogs, the same operation was performed but, in addition, talc powder was introduced into the pericardial sac at and around the site of ligation In this group the mortality was 25 per cent In the third group of 16 dogs, adhesive pericarditis was produced first by means of the talc and then, two or three weeks later, the same ligations and divisions were performed In this group there were no deaths These experiments demonstrated the ability of the pericardium to furnish a collateral circulation sufficient to overcome the ischemia produced by sudden, complete ligation of a main branch of the coronary artery, when adhesive pericarditis had been previously established

In order to obtain further evidence upon the extent of collateral circulation from the pericardium, in a fourth group of eight dogs adhesive pericarditis was first produced as described above After 14 to 21 days, the descending branch of the left coronary artery was ligated just below the circumflex branch Two or three weeks after this operation the right coronary artery was ligated in its middle part Following recovery from this operation the circumflex artery on the left was ligated at its origin About 14 to 21 days later the right coronary artery was also ligated near the aorta Thus there was no longer any direct supply of blood to the heart muscle, except through the collateral channels Two dogs survived this extensive series of ligations, they could run and play with other dogs and were apparently well

Robertson¹⁰ reported a series of experiments in which by successive stages the coronary arteries were ligated up to their aortic origin and adhesive pericarditis was produced at the same time Then, to determine the presence of a collateral circulation from any source other than the pericardium he removed the adherent pericardium, following which procedure none of the dogs survived

In 1842 Chevers¹⁰ demonstrated by autopsy material the presence of cardiac hypertrophy associated with adherent pericarditis only when additional pathologic changes existed which could account for the hypertrophy Hosler and Williams²¹ have shown from animal experiment and the analysis of 4,400 autopsy reports that adhesive pericarditis itself is usually silent and innocuous, does not play a significant rôle in the production of cardiac hypertrophy, and does not cause circulatory embarrassment unless it is extensive enough to cause cardiac angulation, torsion or compression

It is necessary at this point to emphasize the difference between constrictive pericarditis and adhesive pericarditis The two terms are often confused and considered to be identical, but they are, or may be, entirely different The procedure which we advocate is the production of an adhesive pericarditis, and this is accomplished by our technic without producing constrictive pericarditis, as observation of the venous blood pressure at long intervals after operation has demonstrated

As to the normal collateral coronary circulation Wiggers,⁶ in a com-

prehensive survey and a critical reevaluation of available evidence, concludes that "the coronary anastomoses in normal hearts apparently have no functional value. This does not preclude the increase in calibre of the potential communications, or the development of a new system of vessels which can furnish adequate nourishment under pathological conditions. As a result of the gradual narrowing of a coronary branch, the pressure within this branch decreases and the pressure gradients between intercoronary and extracoronary channels are favorable for a continuous flow towards the ischemic area during systole as well as diastole."

Augmentation of the coronary circulation by adhesive pericarditis may occur in any or all of three ways (figure 3) (1) by the formation of new

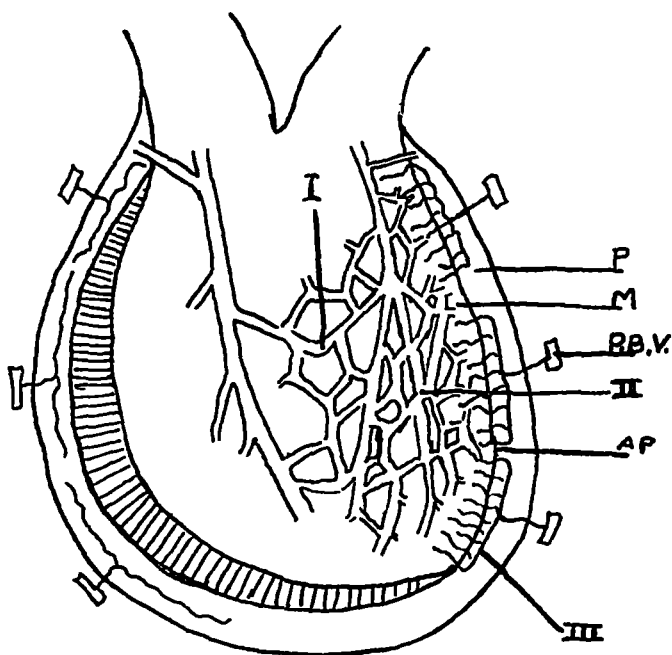


FIG 3 This diagram illustrates the augmentation of the coronary circulation by adhesive pericarditis (1) New channels form between the main coronary arteries (2) Proliferation and dilatation of already existing intercoronary channels (3) Formation of new extracardiac channels from the pericardium

P, pericardium, M, myocardium, P B V, pericardial blood vessel, A P, site of adherent pericardium to epicardium

channels between the main coronaries, (2) by dilatation and proliferation of already existing intercoronary channels, or (3) by the formation of new extracardiac channels from the grafted pericardium

OPERATIVE TECHNIC

In accordance with recent terminology we have called the production of adhesive pericarditis by operation, cardio-pericardiopexy. It is a simple operation and can be done in about 20 minutes. The procedure is as follows: an incision approximately three inches long is made over the left fifth costal

cartilage, the median end of the incision being at the costosternal junction. The incision is carried down to the costal cartilage. The perichondrium is incised and stripped from the cartilage anteriorly and posteriorly and about one and one-half inches of the cartilage is removed. The posterior perichondrium is incised for one and one-half inches, exposing the anterior mediastinum. Care is taken not to injure the internal mammary artery, which is now exposed. This artery and vein are retracted mesially. This approach is over the so-called free space and the pleura does not usually appear in the field. However, if it is present, it is gently retracted laterally, exposing the pericardium. The pericardium is picked up by hemostats and a one inch incision is made through an avascular area. A small rubber suction tube is inserted into the pericardial sac and any fluid present is removed. Five cubic centimeters of a 2 per cent solution of novocain are then dropped onto the epicardium to prevent fibrillation. This is allowed to remain in the pericardial sac for about four or five minutes and is then removed by suction. The heart is now palpated with one finger inserted into the pericardial sac. Any infarcts or scars are noted, as well as the presence or absence of adhesions of the pericardium to the epicardium. Approximately two drams of sterile, dry talc powder is now spread over the anterior surface and the inferior and left borders of the heart. The powder may be applied by a spatula or by an atomizer. The pericardial incision is now incompletely closed with No. 0 plain catgut. The posterior perichondrium is closed with fine catgut. The muscles of the chest wall, which were severed in the approach, are now approximated and the skin is closed. No drain is inserted.

The medical problems which arise in connection with the surgical treatment of coronary disease include the following: (1) the establishment of criteria for the selection of patients, (2) preoperative study and preparation, (3) postoperative management, and (4) the evaluation of results.

SELECTION OF CASES

During the course of study of a new method such as cardio-pericardiopexy the selection of cases must be conservative and the criteria upon which selection is based must be made extremely rigorous.

At present we have limited ourselves to cases which can meet fully the following criteria. The first is a definite and clearly defined anginal syndrome, pain of characteristic nature and distribution, and particularly with a definite relationship to effort. This criterion is purely subjective but it is basic.

Of equal importance is objective evidence of coronary and myocardial disease in the form of positive physical, electrocardiographic and roentgen-ray findings.

Beyond these basic criteria we have added the following: the absence of improvement after fairly prolonged medical treatment and an extreme de-

gree of disability, corresponding at least to Class III of the Heart Association Classification, necessitating greatly limited physical activities. From the point of view of gaining a livelihood, most of our patients were in Class IV, unable to walk more than a few hundred feet without anginal pain and, therefore, completely crippled. Thus we have endeavored to take only cases that might have something to gain and practically nothing to lose.

A previous coronary occlusion is not considered a contraindication, rather the contrary as it constitutes definite proof of coronary disease. However, sufficient time must have elapsed to permit healing of the infarct, with no evidence of an active process still going on, and a further period of time is necessary to establish the fact that the patient still suffers from extreme limitation due to the myocardial condition. A fibrous scar following an infarct may not, of course, be influenced by any proffered new blood supply from pericardial adhesions or other sources, but we believe that bringing a fresh blood supply to other areas of the epicardium will be profitable.

Congestive heart failure is a contraindication to operation if there are any clinical evidences of passive congestion in the form of moisture at the lung bases, enlargement of the liver, or edema. Such findings increase the operative risk beyond a reasonable or safe point in our estimation. On the other hand, in some cases in which the dynamics of the circulation have been upset as shown by slowing of the circulation time and a rise in venous pressure, these manifestations have not been accepted as contraindications if the clinical findings were otherwise satisfactory. In two cases there were physical signs of congestive heart failure which had developed after previous coronary disease. Operation was performed after a preliminary period of treatment consisting of rest, digitalization and diuretic measures so that the patients came to operation after a period of complete freedom from the usual signs of passive congestion. Under these circumstances operation was well tolerated.

PREOPERATIVE STUDY

Our preliminary routine begins with a cardiological examination consisting of a detailed history, complete physical examination, routine electrocardiograms including at least two chest leads (CR-2 and CR-4) and roentgen-ray study (two-meter chest film and fluoroscopy). On the basis of this preliminary examination cases were selected and were then subjected to further study: determination of the circulation time, of the venous pressure by the direct method, and special electrocardiographic studies if ordinary records did not show positive findings.

It is of interest to note that in cases presenting the picture of pure anginal syndrome without apparent passive congestion on physical examination, we have found some slowing of the circulation time.

The determination of the venous blood pressure by the direct method showed some elevation in occasional cases. Our chief interest in the venous

pressure was to determine the preoperative levels for comparison in the future. Any obstruction to the return flow to the heart by reason of pericardial bands or adhesions should be detected relatively early by a rise in the venous pressure. It is our present belief that any difficulty in the future from pericardial bands or the like is not a real danger with this method. The adhesions which we seek to produce are limited to the area of application of the powder and do not tend to produce bands which have a constricting or tortional effect. So far our observations directly substantiate this belief, as the venous pressure after operation has in general remained normal or become somewhat lower than before, without any tendency to an abnormal rise in venous pressure during our period of observation, now extending to over three years.

Electrocardiograms taken at rest have given positive evidence of coronary arterial disease in a fair proportion of cases. In some of our patients we have been able to secure records from other observers taken during acute coronary occlusions in the past. If a record taken at rest lacks distinctive changes, two methods are open to permit more positive findings. One of these, exercise tests followed by serial electrocardiograms, has not been used as our patients were too ill to permit physical activity pushed to this degree. We have, therefore, used an anoxemia test which has given positive findings which fulfill our basic criteria when electrocardiograms at rest were not conclusive.

We have used a face mask which covers both the nose and the mouth, with a valve in the mask so that expired air is released at once. There is no dead space between the mouth and the valve so that the patient does not rebreathe any of his own CO_2 . The mixture we use consists of 10 per cent oxygen and 90 per cent nitrogen. A control electrocardiogram is taken with a preliminary blood pressure reading. Then 10 per cent oxygen administration is begun, and every five minutes we take an electrocardiogram and blood pressure reading. The patient signals promptly if anginal pain develops or any other acute distress and, in that event, the test is stopped at once. If no adverse symptoms develop, the inhalation of 10 per cent oxygen is continued for 20 minutes. The patient is then given pure oxygen for three minutes and another final control electrocardiogram is recorded. In several of our cases the patient was unable to take 10 per cent oxygen for more than five or ten minutes without acute distress. In no cases have we observed the development of alarming symptoms or more than transient distress, but the occurrence of such symptoms is not acceptable as evidence of a positive test. We consider a positive test the occurrence of changes in the electrocardiogram of characteristic types: shifting of the S-T segment and variations in the amplitude and direction of the T-wave due to a subnormal state of oxygenation of the myocardium during the test. We have considered such changes as evidence of a subnormal coronary blood supply (figures 4, 5, 6, 7).

Our preoperative study is completed by tests which are intended to rule out the possibility of any active myocardial process due to a recent occlusion. In two of our earlier cases we believe that this feature of the study was not adequately covered, and it is highly important. The white blood count is

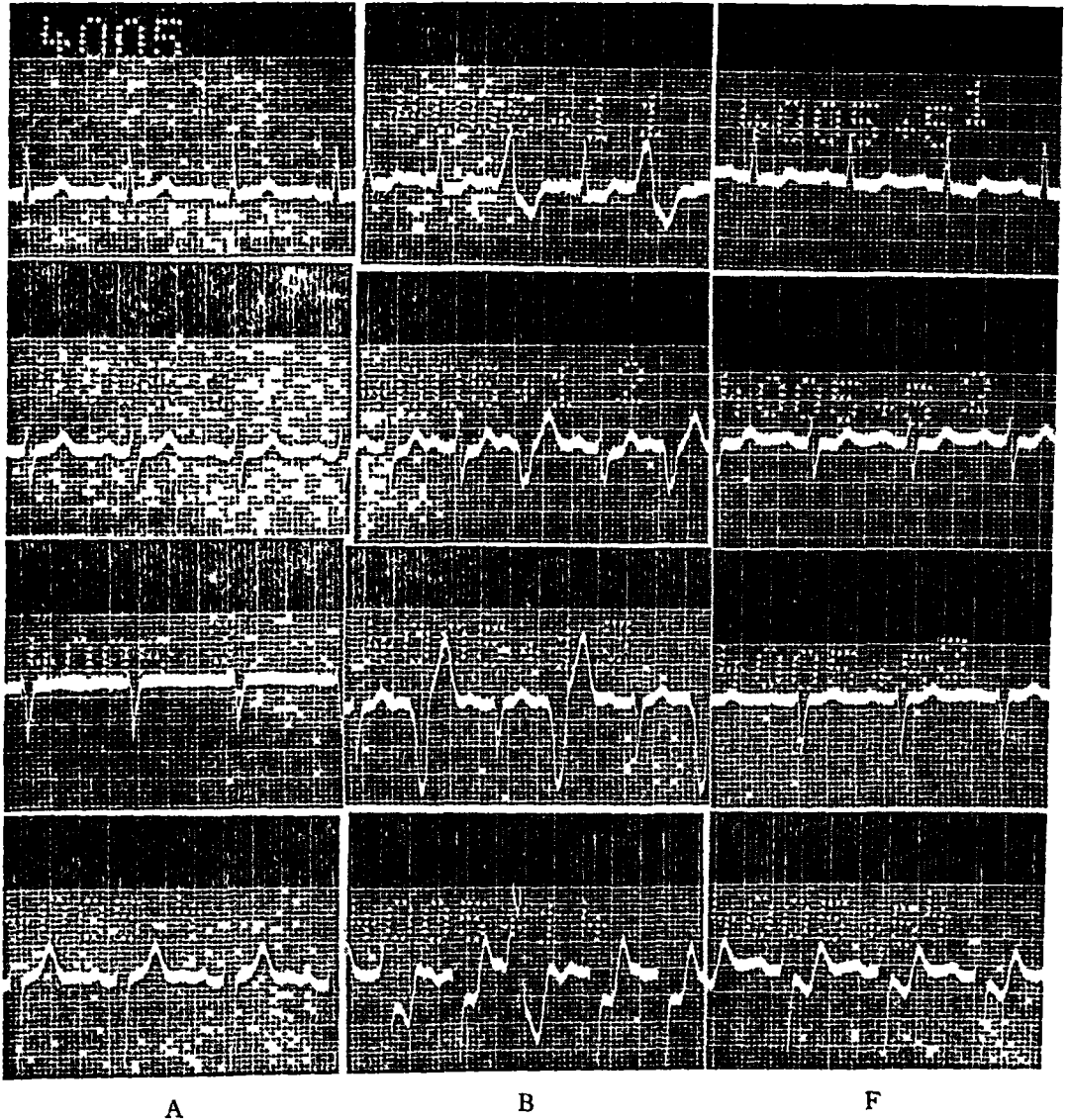


FIG 4 Anoxemia test, case 8. A, control. B, after 5 minutes of 10 per cent O_2 . Note lowering of the RS-T segments in Leads I, II and IV. F, after 3 minutes of pure O_2 . This patient was not able to tolerate 10 per cent O_2 for more than 5 minutes.

helpful, but the red cell sedimentation rate is more sensitive and both should be done and should remain normal for at least two determinations about a week apart. In addition we have taken serial electrocardiograms at intervals of a few days to determine that the record is stabilized in its present form. These precautions tend to prevent, as far as may be possible, bringing a patient to operation with an infarct only partially healed.

Preoperative medication must vary according to the individual indications. In two of our patients who came to us in congestive heart failure we have used digitalis and the usual methods of treatment until all signs of passive congestion were cleared up. As a routine we give quinidine sulfate 0.20 gm or gr. iii at intervals of four hours for several doses immediately preceding operation, the last dose timed within two hours of operation. This is intended to minimize the danger of the development of ectopic rhythms during operation. Preoperative sedation consisted of morphine

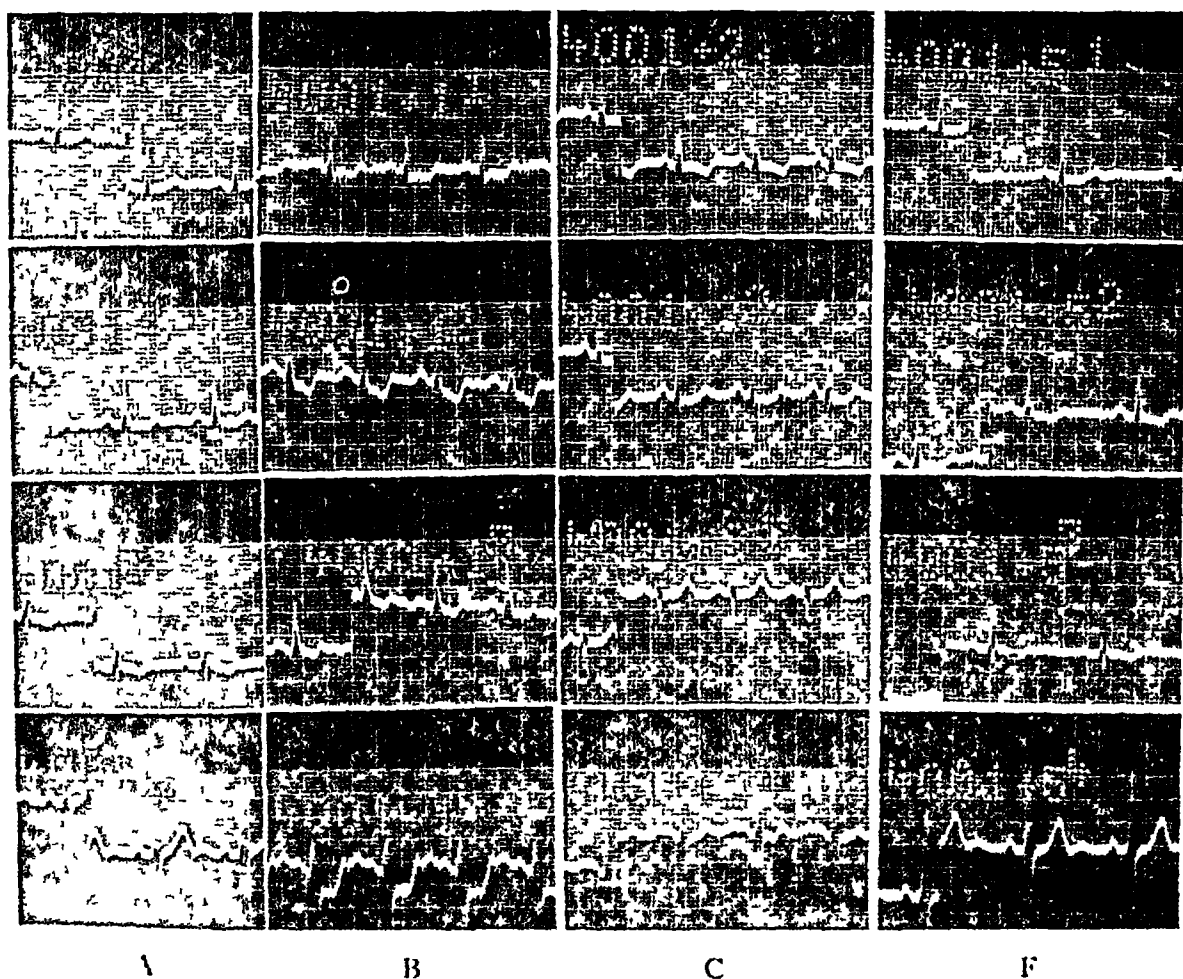


FIG. 5. Anoxemia test, case 10. A, control. B, after 5 minutes of 10 per cent O_2 . C, after 10 minutes of 10 per cent O_2 . F, after 3 minutes of pure O_2 . This patient was not able to tolerate 10 per cent O_2 for more than 10 minutes.

gr. $\frac{1}{4}$ to $\frac{1}{16}$, and atropine was given immediately before operation in doses of gr. $\frac{1}{100}$ and again immediately after operation.

The anesthesia used has been cyclopropane and oxygen, giving approximately 25 per cent cyclopropane and 75 per cent oxygen. If there were any signs of ectopic beats during operation, an extra dose of atropine gr. $\frac{1}{100}$ was given at once. Electrocardiograms were taken at short intervals during operation and only occasionally have we observed ventricular premature beat. Only rarely did two occur in succession and at no time have we had

evidence of ventricular tachycardia. As far as we can determine, this form of anesthesia is preferable for our purpose because of the large amount of oxygen which can be given and we do not feel that the anesthesia tends, under the circumstances in which we have used it, to favor the production of ectopic rhythms.

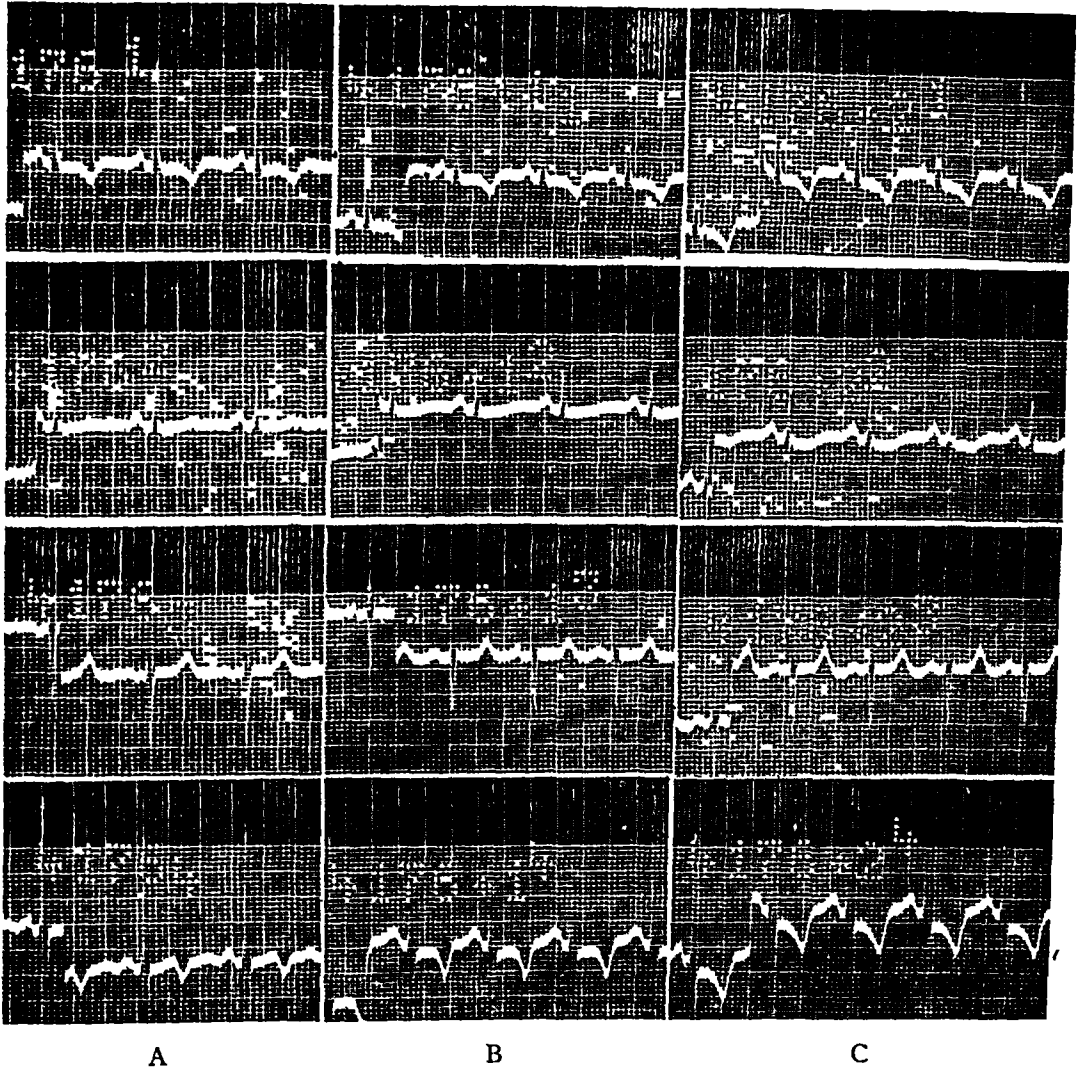


FIG 6 Apnoeemia test, case 7. A, control. B, after 5 minutes of 10 per cent O_2 . C, after 10 minutes of 10 per cent O_2 . In Lead IV the depression of the T-wave becomes more marked and the S-T segment is lowered.

POSTOPERATIVE COURSE

There is a febrile reaction with temperature reaching approximately $103^{\circ} F$ by the second or third day after operation. The elevation of temperature subsides gradually, in all lasting between 10 days and two weeks. In one case the temperature reached $104^{\circ} F$ and did not fall entirely to normal until three weeks had elapsed. No special cause could be found for

this prolongation of the febrile reaction, and the patient (Case 5) made a good recovery

A pericardial friction rub is audible fairly promptly. We have not been insistent in attempting auscultation during the first day so as to avoid interfering with the operative wound. A friction rub has been heard definitely

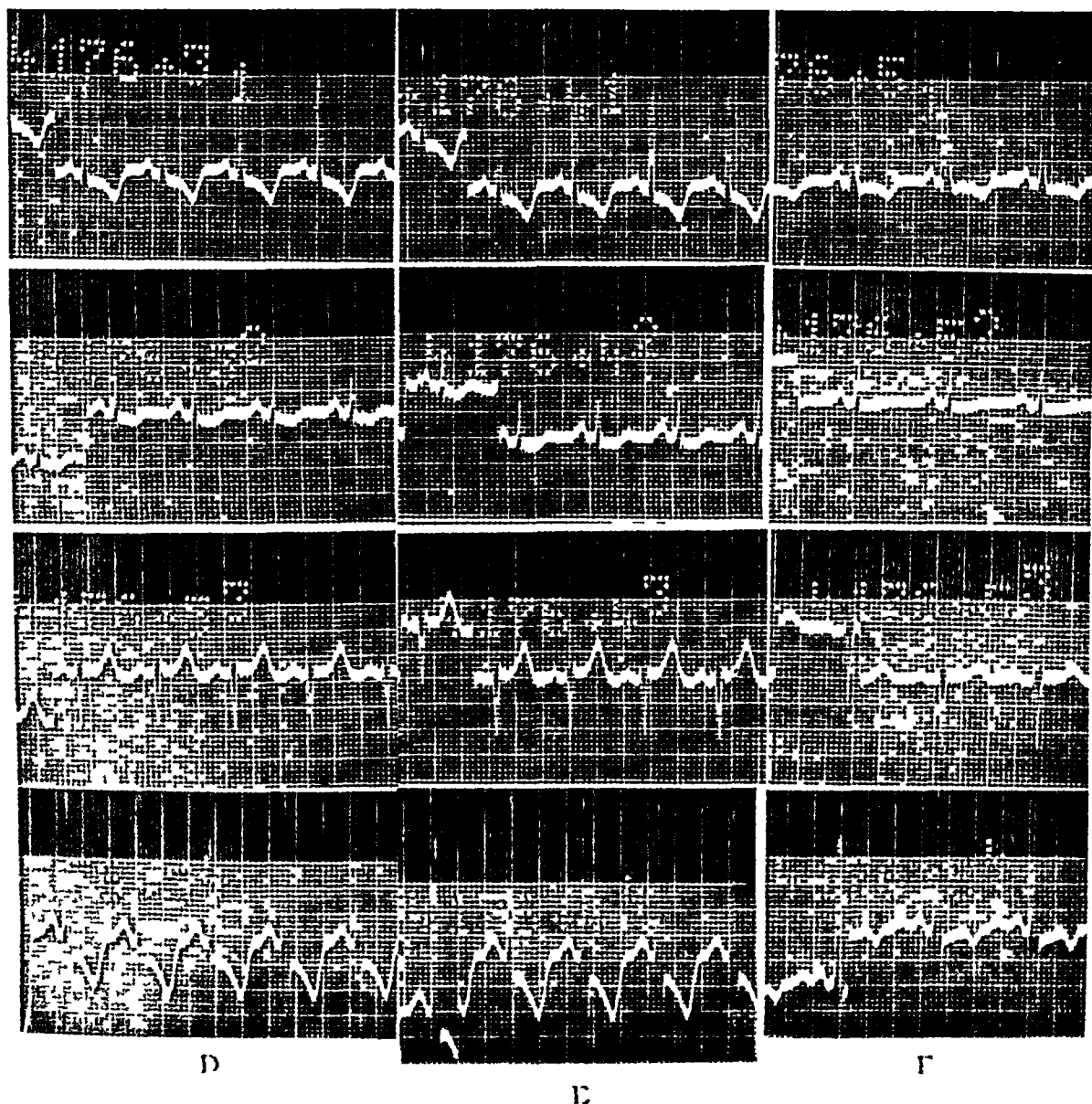


FIG. 7. Anoxemia test case 7 continued. D, after 15 minutes of 10 per cent O_2 ; E, after 20 minutes of 10 per cent O_2 ; F, after 3 minutes of pure O_2 .

on the second day and as the compresses are made smaller after the third day, it is heard over a wide area, practically the entire precordium, and persists upward of three weeks.

Within 24 to 36 hours of the operation we have regularly observed evidence of consolidation of the left lower lobe and in the first case we were troubled by what appeared to be the development of postoperative pneumonia.

The physical findings are characterized by striking bronchial breathing and clear, high-pitched expiration, but with practically no râles or evidence of moisture in the alveoli. This change in the breath sounds is noticeable chiefly in the left axilla and below the angle of the left scapula. There is no cough or expectoration and the patient does not appear ill, as one might expect from the level of temperature and the bronchial breathing. Further observation in subsequent cases has made it clear that we are dealing with an inflammatory reaction, involving the contiguous tissues and lobe of the lung and characterized by evidence of consolidation but without exudate in the alveoli. For this we have used the term interstitial pneumonitis. The physical signs clear up within a week as a rule.

We have considered the possibility of compression of the lung by a pericardial exudate, but as far as we can determine by physical and roentgen-ray findings there is no demonstrable amount of fluid in the pericardial sac.

Inflammatory changes may involve the pleura and in two cases we have observed a small effusion on the left. This has been followed by adhesions in the left costophrenic angle, slightly limiting the movements of the diaphragm, such as we usually see after old attacks of pleurisy.

There is abundant roentgen-ray evidence of mediastinitis (figures 8A, 8B, 8C). Our first chest film is taken the day following operation and regularly shows enlargement of the mediastinal shadows which bulge out on each side during the first week of the postoperative period or a little longer. Clinical evidence of this was present in two cases in the form of mild dysphagia which lasted for about four days. Serial roentgen-ray films show regression of the mediastinal shadows, although they remain somewhat heavier than normal for several weeks after operation, clearing up slowly.

The electrocardiographic changes (figures 9 and 10), which are the subject of a separate communication, are characteristic of an acute pericardial reaction. There is concordant shifting of the S-T segment in the limb leads. In some cases the S-T segment in Lead III has shown a downward shift.

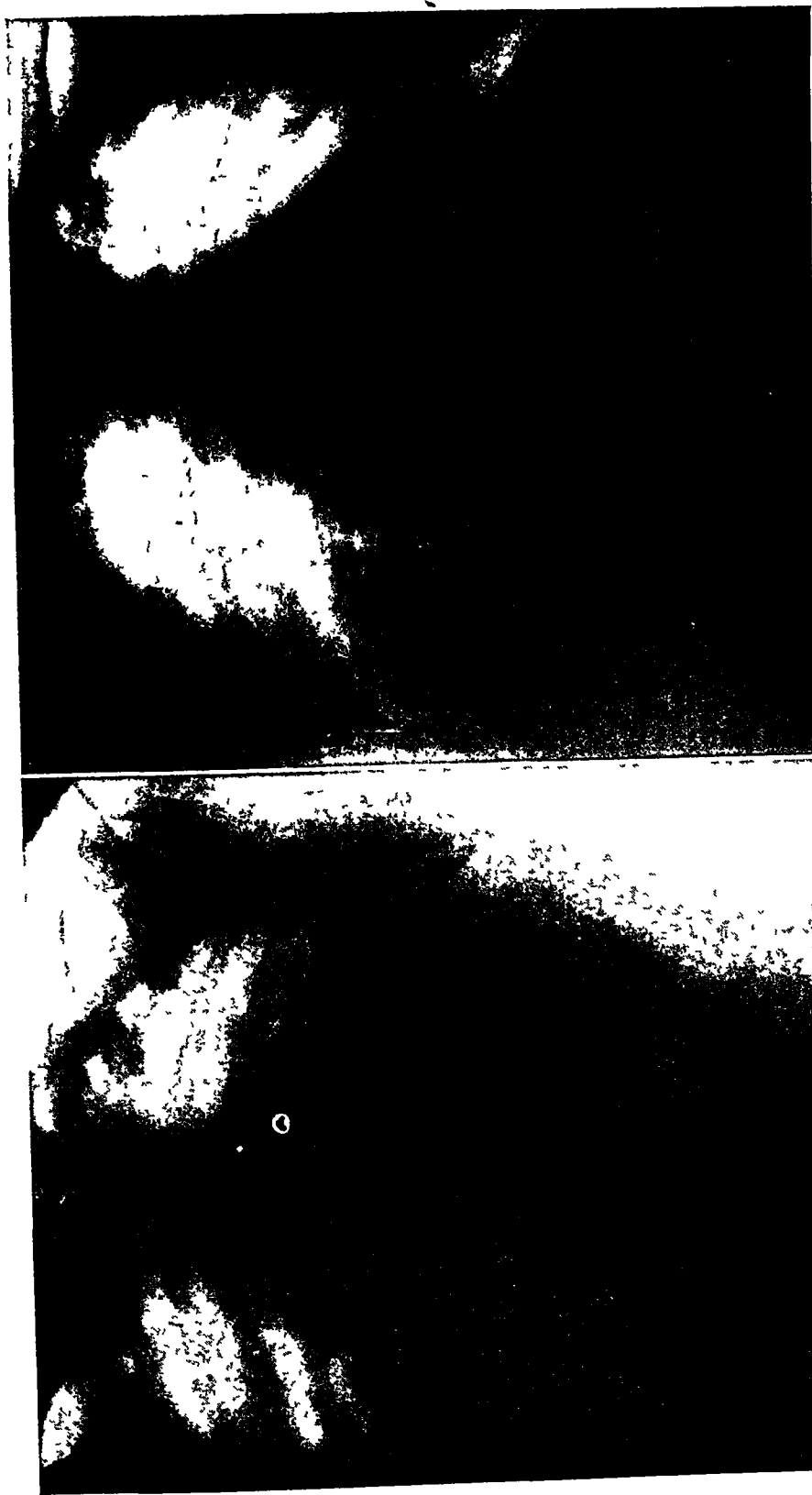
Postoperative medication has consisted of oxygen given as a routine during the first two days by double nasal catheter of the Bullowa type. There has been no respiratory distress and the color has remained normal, but it appeared reasonable to supply oxygen in order to spare the heart as much as possible. Sedatives have been used to control pain and in some cases to control cough. Moderate doses of morphine have sufficed and have not been needed beyond the second or third day. The need for continuing quinidine after operation has not been evident. As a rule ectopic beats or rhythms have not been observed. In our first case the appearance of bronchial breathing with the rise in temperature led us to use sulfapyridine (then available for investigational use under the name dajenan). Although we are not thoroughly convinced that chemotherapy is essential, it has

seemed wise to use it in order to limit any possible inflammatory complications. For this reason we have used moderate doses of sulfathiazole during the first three to five days until we are assured that the regression of the physical signs and the control of temperature are satisfactory.



FIG. 8A. Roentgen-ray film of patient H. K. taken with a portable machine two days before operation. The portable machine was used so there could be a comparison with the pictures taken after operation.

Our clinical material has offered extra hazards because of the extreme degree of disability and recurrent anginal pain under the slightest provocation before operation. In spite of these undesirable factors in our clinical material the postoperative course has been fairly uneventful. The interstitial pneumonitis does not cause respiratory distress or cyanosis and cough requires only occasional medication. The patient does not manifest general



B

C

FIG 8B Patient H K (same as figure 8A) This portable roentgen-ray was taken two days after operation There is considerable increase in the width of the mediastinum There is some increased density of both lung bases Notice the inflammatory reaction spreading from the mediastinum out into the interlobar fissure on the right side

FIG 8C The same as figure 8B, but taken nine days after operation The mediastinum has decreased in size The inflammatory reaction around the mediastinum is not as pronounced and the physical signs at this time were normal

100

B

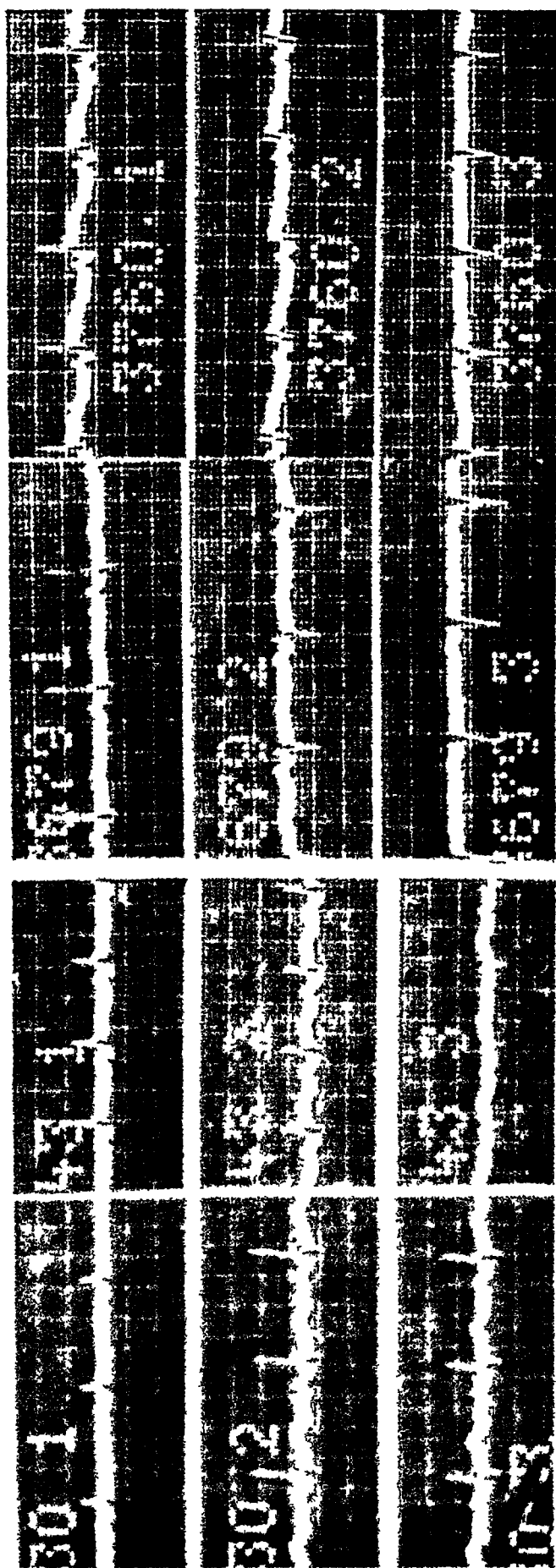


Figure 10. A series of nine waveforms (3011-3019) showing the RS-F segments due to the periodicity of the RS-F segments. The waveforms are arranged in a 3x3 grid. The top row shows waveforms 3011, 3012, and 3013. The middle row shows waveforms 3014, 3015, and 3016. The bottom row shows waveforms 3017, 3018, and 3019. The waveforms are labeled on both the left and right sides of the grid.

illness or depression such as we would expect in pneumonia and there is a marked contrast between the objective and the subjective findings

There is some distress in moving the left arm or shoulder which is due to the attachment of the pectoral muscles in the neighborhood of the operative wound. This has been controlled by mild sedatives but may persist for several weeks after operation. Painful left shoulder may develop as a late manifestation in coronary disease and is a familiar clinical entity, particularly in cases that have formerly suffered occlusion and infarction. This may be a complicating factor as far as left shoulder pain is concerned in our patients, but we have the distinct impression that local conditions affecting the pectoral and other muscles of the shoulder girdle adequately explain the symptoms. Distress from this source has not hampered recovery and clears up within a few weeks.

EVALUATION OF RESULTS

In the selection of cases we have been guided by the principle that operation is justified if the patient has nothing to lose and possibly something to gain. Thus our group of cases represents cardiac derelicts with advanced coronary disease and under ordinary circumstances a hopeless prognosis. We have been surprised and encouraged to note that they tolerated operation so well and that the postoperative course went on as smoothly as it has done in most of our series.

Three patients died a short time after operation, one within a few hours and the other two on the second day. A fourth patient died three weeks after operation. In the patient who died within a few hours we were dealing with recurrent anginal pain at rest which had kept the patient bedridden for some time. We do not believe that we were sufficiently alert to the fact that an active process was present and subsequently in other patients we were able to rule this possibility out by additional serial determinations of the sedimentation rate and serial electrocardiograms.

In one patient dying on the second day an autopsy could not be secured, but we suspected either a fresh coronary accident or a pulmonary embolus.

Our total series now numbers 13 * and of the nine remaining patients none has failed to secure some relief, which has been striking in several cases, permitting a return to normal exercise capacity. The results are of greater interest in proportion to the length of time that has elapsed since operation. Our first case now dates back over three years and the improvement is marked (estimated by the patient as 75 per cent) and in our second case, dating back nearly two and a half years, the patient shows marked improvement and has a normal exercise tolerance.

The clinical notes herewith give the details of each case as far as our period of observation extends.

* Since this report was received three additional patients have been operated upon with excellent results in all up to the present time.

CASE REPORTS

Case 1. O. S., business man aged 39, was first seen in September 1936, during the acute phase of a coronary occlusion with typical electrocardiographic evidence of a complete bundle branch block. Pain was so severe that it could not be controlled by morphine and required para-vertebral block October 1, 1936. Thereafter he was crippled by anginal pain and when seen again in November 1938 was stopped on an average of three times within a short block by acute chest distress which also came on after exertion. Electrocardiogram on November 22, 1938 showed slight depression of T₁ and P wave lacking in Lead CR-2. Cardio-pericardiopexy was performed November 25, 1938. There was electrocardiographic evidence of the usual pericardial reaction, and sharper depression of T₁. The venous pressure 18 months after operation was 88 mm H₂O and two years after operation was 70 mm H₂O. The clinical course since operation has been as follows. Following operation the patient increased his activity without precordial distress until February 20, 1939 when, after shoveling snow, he had severe chest pain. He gradually became active again and in June 1939 returned to severe chest pain following overexertion playing bill. At present he resists chest pain only when he lifts anything heavy or overexerts himself. He can walk more than a mile without distress and if he does not hurry he can be active all day without symptom. Chest distress tends to come on more easily after a meal. He feels that he is greatly improved and estimates the improvement as 75 per cent compared to his state of complete disability between 1936 and 1938. We estimate this as a marked improvement, not more than three years following operation.

Case 2. B. S., a farmer, man aged 47, was first seen December 1938. In November 1938 a coronary occlusion had occurred for which the patient was admitted to Lake Hill Hospital. In December 1938 the electrocardiogram showed an anterior bundle branch block. Anginal pain was so severe and frequent that he was unable to leave his bed, a condition which deepened to an apyrexial state. Before operation the pain was relieved by combining 44 mg. of morphine with 10 mg. of atropine. Cardio-pericardiopexy was performed December 11, 1938. In February 1939 he was able to walk five or six blocks at a time without distress and to spend most of his day in bed. In July 1939 he was doing very well, walking on an even surface for 10 to 15 miles daily, and he felt much better than he had before operation. In May 1941 a severe coronary occlusion occurred which was fatal. In July 1941 the patient was found dead of heart attack after a severe attack of chest distress. Recovery from the operation was complete. The electrocardiogram showed a normal P wave. In May 1941 a severe coronary occlusion occurred which was fatal. In July 1941 the patient was found dead of heart attack after a severe attack of chest distress. Recovery from the operation was complete. The electrocardiogram showed a normal P wave.

disease followed by congestive failure which did not respond to medical treatment until after operation. The degree of improvement may be considered moderate as the patient still needs some digitalis to carry on in comfort, but he follows a full program of work.

Case 4 H E O, salesman, aged 50. On August 17, 1938, a coronary occlusion occurred with anterior wall infarct and an electrocardiogram submitted, taken September 19, 1938 showed some depression of T_1 and T_2 . In April, 1939 there was frequent chest pain occurring at rest and aggravated by exercise. Cardio-pericardiopexy was performed May 3, 1939. The postoperative course was complicated by wound infection by a gas forming bacillus later identified as *Bacillus welchii*. Local healing was slow but the general condition remained satisfactory. In May 1941 the patient reported complete absence of chest pain. At his best before operation he was able to walk four or five blocks and, therefore, improvement may be considered marked, with complete relief from angina.

Case 5 G A, housewife, aged 36. This patient complained of frequent chest pains and fainting attacks. The electrocardiogram at rest showed a low T_2 , and under anoxemia there was a further flattening of the T-wave in this lead. The clinical picture was not typical and after a first admission in February 1939 operation was withheld. Symptoms, however, increased and after readmission in July 1939 cardio-pericardiopexy was decided upon and performed July 13, 1939. The postoperative course was uneventful, except for the fact that fever lasted for a longer period than usual, up to three weeks. Upon discharge on August 4, 1939, there was marked subjective improvement, and this has been maintained to date. In July 1941, the patient had to go back to business on account of the illness of her husband. This involves commuting from New Jersey daily, leaving home at 7:30 a.m. with a 15 minute walk on arriving in the city and a similar one to get home at night. Chest distress occurs after marked excitement or if she hurries, but she is able to carry on. There is a great deal of fatigue toward the end of each week, but she estimates her improvement as 70 to 80 per cent now permitting gainful occupation under severe strain, quite impossible before operation. Therefore the degree of improvement may be considered marked.

Case 6 J D, machinist, aged 59 years. The chief complaint was substernal, burning pain associated with effort. The electrocardiogram August 3, 1939 showed depression of T_2 and T_3 . During the anoxemia test the RT segment in Lead I was lowered, T_1 became diphasic, and with further anoxemia the foot-point of T_2 became elevated. Cardio-pericardiopexy was performed August 7, 1939. Venous pressure before operation was 130 and after operation on August 9, 210 mm H₂O. Shortly after operation dyspnea developed and death occurred on August 9, 1939. Autopsy showed a recent infarct in the posterior wall of the left ventricle extending from a point 2 cm above the apex to the base of the ventricle. Death occurred as a result of fresh coronary occlusion with acute dilatation of the left heart and multiple pulmonary infarcts resulting from mural thrombosis of the pulmonary artery.

Case 7 J B, bartender, aged 52. For the preceding three or four years the patient had complained of pain in the left chest and left arm, progressively worse, associated with hypertension. He had been overweight, reaching 240 pounds, but had dieted down to 200 pounds when first seen in August 1939. On August 18, 1939 the electrocardiogram showed a small diphasic T_1 and in the course of the anoxemia test there were additional changes: sagging of the RT segment in Lead II and later marked depression of T_1 which returned toward normal after inhalation of pure oxygen. Cardio-pericardiopexy was performed August 18, 1939. Venous pressure before operation was 190 mm H₂O. Three days after operation it was 260 and 12 days after it was 180 mm H₂O. Postoperative course was uneventful. Since operation the hypertension has persisted but there has been complete relief of the anginal pain. He can now walk up to a mile at a time without distress and is back at work.

Case 8 M W, business executive, aged 59 years. He had been well up to the age of 56. In July 1936, after swimming, he had prolonged and severe chest pain. After that he was able to walk only about two or three blocks and occasionally four blocks, but was severely limited by anginal distress. The electrocardiogram at rest did not show distinctive changes, but under anoxemia there was depression of the RT segment in Leads I and IV with frequent ventricular premature contractions. T₁ became quite diphasic and the patient's distress was so acute that 10 per cent oxygen could not be continued for more than five minutes. Cardio-pericardiopexy was performed August 21, 1939. The venous pressure after operation on August 23 was 180, on August 30, 120 and on September 12, 150 mm H₂O. Severe attacks of chest pain lasting 15 to 20 minutes occurred at various intervals before operation, and since operation he has had no attacks. He is now able to walk up to 15 blocks at a time without distress, although slight chest distress does occur after climbing two flights of stairs. He estimates his improvement as 90 per cent and is now back at work.

Case 9 I P, ticket seller, aged 54, complained of substernal and precordial pain radiating to the left shoulder and arm during the preceding two years. On August 17, 1939, walking slowly up 10 steps caused mild substernal pain radiating to the left arm. The electrocardiogram at rest showed depression of the T-wave in all the limb leads and diphasic T₁. Under anoxemia this depression became more marked with lowering of the foot-point of the T-wave particularly in Leads I and II. Cardio-pericardiopexy was performed October 18, 1939. The venous pressure before operation on October 17 was 170 mm H₂O and was higher after operation, reaching 200 on October 18, 1939. On October 19, the general condition appeared satisfactory with no difficulty in respiration but later the same day the venous pressure was found elevated (230 mm H₂O). On October 20 the patient complained of pain and restlessness. The venous pressure was found to be 240 mm H₂O and death occurred on this day, apparently of acute congestive heart failure. Autopsy was not permitted.

Case 10 O E W, physician, aged 50 years. In November 1934, at the age of 46, he first noted chest distress while walking, which at first was only occasional and mild, after unusual exertion. This became progressively worse so that in July 1939, on an empty stomach, he could walk slowly about 150 feet but faster walking stopped him within this distance. At rest the electrocardiogram did not show distinctive changes, but after exercise there was a definite lowering of the foot-point of T₁ and T₂. On November 7, 1939 one flight of stairs produced severe anginal pain. Cardio-pericardiopexy was performed November 8, 1939. Before operation the venous pressure varied between 155 and 160 mm H₂O. After operation on November 9 it reached 165 and once after getting up on November 14, 230 mm H₂O. After that the venous pressure was between 95 and 110 mm H₂O. Upon discharge from the hospital he was able to walk up two flights of stairs with only slight distress. Since then he has resumed practice limited to eye, ear, nose and throat work, with occasional tonsillectomies and minor nasal operations. Walking causes chest distress but he has resumed practice which he was unable to carry on before operation. We believe there has been a definite improvement but of moderate degree.

Case 11 J B, mechanic, aged 64. The patient complained of chest pain during the preceding three years with much limitation of activity, Class III. The electrocardiogram showed evidence of atypical intraventricular conduction defect. Cardio-pericardiopexy was performed December 8, 1939. The postoperative course at first did not show unusual features, but tachycardia, weakness and air hunger developed on December 24, 1939, with collapse, and the patient died on December 30, 1939. Postmortem examination showed a fresh infarct in the posterior wall of the left ventricle. There was a complete obliteration of the pericardial sac with the pericardium adherent to the myocardium. The pericardial vessels were congested and engorged. Injection of one of the pericardial vessels with India ink demonstrated the passage of the ink into the myocardial vessels.

Case 12 W H S, clerk, aged 48 The patient was completely crippled by anginal pain recurring at rest while in bed The electrocardiogram at rest showed practically flat T-waves in the limb leads He could tolerate the anoxemia test for only five minutes and then showed some lowering of the RT segment in Lead I The venous pressure was elevated before operation, on January 26 it was 340 and on January 28, 1940, 260 mm H₂O Cardio-pericardiopexy was performed January 30, 1940 Death, which occurred about half an hour after operation, appeared to be due to ventricular fibrillation Autopsy showed marked calcification of both main coronaries with complete occlusion of both these arteries There were several old infarcts and one very recent infarct in the left ventricular wall

Case 13 H K, furrier, aged 47 years At the age of 44 pain in the left chest occurred On January 16, 1939, the symptoms of coronary occlusion were so severe as to require hospitalization for six weeks Thereafter his activities were limited by chest pain (Class II) December 8, 1940, a second coronary occlusion occurred and he was in the hospital about 7 weeks Following this attack pain on effort was more severe, causing greater limitation (Class III) The electrocardiogram showed a low T₁ and diphasic T-wave in Lead CR-4, without marked changes during anoxemia Cardio-pericardiopexy was performed March 7, 1941 The venous pressure on March 5 was 120 and on March 6, 115 mm H₂O After operation the venous pressure recorded on March 9 was 90, on March 17, 120, and on March 22, 80 mm H₂O In May 1941, T₁ was sharply inverted and T₂ small and diphasic, but the exercise tolerance showed marked improvement He was able to walk up to a mile without chest distress The period since operation to date has only been four months, but so far the degree of improvement is marked

If the improvement is graded as follows, + slight, ++ moderate, and +++ to ++++ marked, these results from the clinical point of view may be summarized as follows

Case	Time Elapsed Since Operation	Clinical Result
1	2 yrs 8 mos	+++
2	2 yrs 6 mos	++++
3	2 yrs 4 mos	++
4	2 yrs 2 mos	++++
5	2 yrs	+++
6	—	died
7	1 yr 11 mos	+++
8	1 yr 11 mos	+++
9	—	died
10	1 yr 8 mos	++
11	—	died
12	—	died
13	4 mos	++++

In all, four cases have died, two show moderate improvement, and seven show marked improvement

SUMMARY

Cardio-pericardiopexy, or the production of adhesive pericarditis, can be accomplished regularly by the introduction of sterile talc into the pericardial sac, and the technic of the operation has been described

Animal experimentation has demonstrated the ability of the pericardium to furnish a collateral circulation to the myocardium, sufficient to overcome

the ischemia produced by sudden complete ligation of a main branch of the coronary artery when adhesive pericarditis had been previously established

Cardio-pericardioplexy produces a collateral myocardial circulation by any or all of the following ways (1) formation of new channels between the main coronary arteries, (2) dilatation and proliferation of already existing intercoronary channels, and (3) formation of new extracardiac channels from the newly adherent pericardium

It is entirely possible that the beneficial effects of this operation may be due as much to the formation of intracardiac collaterals resulting from the myocardial reaction as to the formation of new extracardiac collaterals from the adherent pericardium. Although the reaction subsides and the stimulation of the operation ceases, the original impetus may accelerate the process of spontaneous collateral formation to a rate equal to or greater than the occlusive process

The criteria which we have used in selecting these patients for operation have been enumerated. It is hoped that additional experience will enable us to extend the present indications to include a larger group of patients

The preoperative study and preparation of the patients for operation, as well as the postoperative management, have been reviewed

The evaluation of our results is gratifying. A group of cardiac delinquents who were completely incapacitated have been relieved of their anginal pain and have returned to their former occupations. The relief from angina is complete in some and partial in others. No patient in our series has failed to show symptomatic relief and a definite increase in his exercise tolerance

Follow-up examinations of all patients, which include exercise tolerance tests, blood pressure, direct venous pressure, fluoroscopy, roentgen-ray and electrocardiographic examinations, fail to show any evidence of cardiac compression or cardiac hypertrophy due to adhesive pericarditis

The simplicity of the operation and the benefits that have accrued to the patients would seem to warrant further employment of this procedure. It has been performed at our suggestion by one other surgeon with good results*. We feel, therefore, that we are dealing with a method which should give good results in any competent hands

BIBLIOGRAPHY

- 1 ARIEFF, M J, WITUSCHINSKY, W V, and RADINERSON, A B. Über den kollateralen Blutkreislauf im Herzen bei Verschluss der Mündung der Kranzarterien (syphilitische Meso-aortitis) und bei adhasiver Mediastinoperikarditis, *Ztschr f klin Med*, 1936, **CXXX**, 153-162
- 2 BECK, C S. Further data on the establishment of a new blood supply to the heart by operation, *Jr Thorac Surg*, 1936, **v**, 604
- 3 BECK, C S, TICHY, V L, and MORITZ, H R. Production of a collateral circulation to the heart, *Proc Soc Exper Biol and Med*, 1935, **XXXII**, 759
- 4 BERNSTEIN, M, and SIMKINS, S. Use of magnesium sulphate in the measurement of circulation time, *Am Heart Jr*, 1939, **xvii**, 218

* This was a patient of Dr Jacob Burstand who was operated upon by Dr E J Dolan

- 5 BETHUNE, NORMAN Pleural poudrage, *Jl Thorac Surg*, 1935, iv, 251
- 6 BLUMGART, HERMAN, SCHIESLER, M J, and DAVIS, DAVID Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathological findings *Am Heart Jr*, 1940, xiv, 1-19
- 7 BURCHFIELD, H B Adjustment in coronary circulation after experimental coronary occlusion with particular reference to vascularization of pericardial adhesions, *Arch Int Med*, 1940, lxx, 240
- 8 BURWILL, C S Clinical study of adhesive pericarditis, *South Med Jl*, 1931, xxiv, 949
- 9 CAMPBELL, J S Stereoscopic radiography of the coronary system, *Quart Jl Med*, 1929, xxii, 247
- 10 CHEVERS, NORMAN Observations on diseases of orifices and valves of aorta, *Guy's Hosp Rep*, 1935, lxxv, 259-263
- 11 DAVIS, D T, MANSELL, H E, and O'SHAUGHNESSY, L Surgical treatment of angina pectoris and allied conditions, *Lancet*, 1938
- 12 DIETRICH, S, and SCHWIFGK, H Angina pectoris und Anoxia des Herzmuskels, *Ztschr f klin Med*, 1933, cxv, 195
- 13 DRINKER, C K, and FIELD, M E Absorption from pericardial cavity, *Jr Exper Med*, 1931, lvi, 143
- 14 FEIL, J, and BECK, C S Treatment of coronary sclerosis, *Jr Am Med Assoc*, 1927, civ, 1781
- 15 FRIEDBACHER, KARL Experimental collateral circulation of the heart, *Surg, Gynec. and Obst*, 1941, lxxii, 1003
- 16 GREENE, C W, and GILBERT, N C Studies in the response of the circulation to low oxygen tension III Changes in the pacemaker and in conduction during extreme oxygen want as shown in the human electrocardiogram, *Arch Int Med*, 1921, xxvii, 517
- 17 GROSS, LOUIS, and BLUM, LESTER Effect of coronary artery occlusion on dog's heart with total coronary sinus ligation, *Proc Soc Exper Biol and Med*, 1935, xxxii, 1578
- 18 HEINBECKER, P, and BARTON, W A Operation for development of collateral circulation to the heart, *Surgery*, 1939, vi, 648
- 19 HERZOG, R S Electrocardiographic studies of chemical pericardial irritants, *Proc Soc Exper Biol and Med*, 1934, xxxii, 230
- 20 HITZIG, W M, KING, F H, and FISHBERG, A M Circulation time in failure of the left side of the heart, *Arch Int Med*, 1935, lv, 112
- 21 HOSLER, R M, and WILLIAMS, J E The study of cardio-pericardial adhesions, *Jr Thorac Surg*, 1936, v, 629, experimental study of cardio-pericardial adhesions, *Proc Soc Exper Biol and Med*, 1938, xxxiv, 528
- 22 HUDSON, C L, MORITZ, A R, and WEARN, J D The extra cardiac anastomosis of the coronary arteries, *Jr Exper Med*, 1932, lvi, 919
- 23 KAMPMFIER, O F. On the lymph flow of the human heart, *Am Heart Jr*, 1928, iv, 210
- 24 KVALE, W F, and ALLEN, E V Rate of the circulation in the arteries and veins of man, *Am Heart Jr*, 1939, xviii, 519
- 25 LARSEN, KAJ H Om Forandringer i Elektrokardiogrammet Hos Sunde og Syge Under Experimental Iltmangel (On electrocardiographic changes in health and disease under experimental anoxemia), *Ejar Munksgaards Forlag*, 1938
- 26 LESLIE, A, SCOTT, W S, JR, and MULINOS, M G Effect of anoxemia on the electrocardiogram of cats after coronary ligation, *Proc Soc Exper Biol and Med*, 1939, xli, 652
- 27 LEVY, R L, BARACH, A L, and BRUENN, H G Effects of induced oxygen want in patients with cardiac pain, *Am Heart Jr*, 1938, xv, 187
- 28 LEVY, R L, BRUENN, H G, and RUSSELL, N G, JR Use of electrocardiographic changes caused by induced anoxemia as a test for coronary insufficiency, *Am Jr Med Sci*, 1939, cxvii, 241

- 29 LEZIUS, A Die kunstliche Blutversorgung des Herzmuskels, Arch klin Chir, 1937, clxxix, 342
- 30 MAUTZ, F R, and BECK, C S The augmentation of collateral coronary circulation by operation, Jr Thorac Surg, 1937, vii, 113
- 31 MAUTZ, F R Reduction of cardiac irritability by epicardial and systemic administration of drugs as a protection in cardiac surgery, Jr Thorac Surg, 1936, v, 612
- 32 MAY, S H Electrocardiographic response to gradually induced oxygen deficiency, Am Heart Jr, 1939, xvii, 655
- 33 MORITZ, A R, HUDSON, C L, and ORGAIN, E S Augmentation of the extra cardiac anastomosis of the coronary arteries through pericardial adhesions, Jr Exper Med, 1932, lvi, 927
- 34 OCUSNER, A, and DEBAKEY, M Surgical treatment of coronary disease, Surgery, 1937 ii, 428
- 35 O'SHAUGHNESSY, L An experimental method of providing a collateral circulation to the heart, Brit Jr Surg, 1936, xxiii, 665
- 36 O'SHAUGHNESSY, L Surgical treatment of cardiac ischemia, Six cases of cardiomentopexy, Lancet, 1937, i, 185
- 37 O'SHAUGHNESSY, L, SLOME, D, and WATSON, F Surgical revascularization of the heart, the experimental basis, Lancet, 1939, i, 617-621
- 38 RANFY, R B A surgical procedure for the relief of angina, Jr Am Med Assoc, 1939, cxiii, 1619
- 39 ROBB, G P, and WEISS, S Method for the measurement of the velocity of the pulmonary and peripheral venous blood flow in man, Am Heart Jr, 1933, viii, 650
- 40 ROBERTSON, H F The reestablishment of cardiac circulation during progressive coronary occlusion, Am Heart Jr, 1935, x, 533
- 41 SPIER, L C, WRIGHT, I S, and SAYLOR, L New method for determining the circulation time throughout the vascular system, preliminary report, Am Heart Jr, 1936, xii, 511
- 42 THOMPSON, SAMUEL A Development of cardiopericardial adhesions following the use of talc, Proc Soc Exper Biol and Med, 1939, xl, 260
- 43 THOMPSON, SAMUEL A An operation for the relief of coronary artery disease, Quart Bull Sea View Hosp, January, 1940
- 44 THOREL, C J Ergebn allg Path u path Anat, 1903, ix, 673
- 45 WANISLEY, THOMAS Anastomosis of coronary arteries, Quain's elements of anatomy, 11th Edition, 1929, Vol IV, Part 3, Longmans, Green & Co, N Y
- 46 WALL, H C Measurement of circulation time with calcium gluconate in patients receiving digitalis, with electrocardiographic studies, Am Heart Jr, 1939, xviii, 228
- 47 WEARNE, J D, METTIER, S R, KLUMPF, D G, and ZSCHIESCHE, L J The nature of the vascular communications between the coronary arteries and the chambers of the heart, Am Heart Jr, 1933, ix, 143
- 48 WIGGERS, CARL J The inadequacy of the normal collateral coronary circulation and the dynamic factors concerned in the development during slow coronary occlusion, Am Heart Jr, 1936, xi, 641

ELECTROSTETHOGRAPHY. 1. CATHODE RAY VISUALIZATION OF LUNG CHEST SOUNDS *

By F LOWELL DUNN, M D , F A C P , WALTER E RAHM, JR , B S , and
ROBERT M COCHRAN, M D , *Omaha, Nebraska*

THE analysis of sounds and vibrations requires visual methods for detail study. The value of visual methods has been demonstrated in many technical fields. Percussion, palpation and auscultation, being tactile and aural methods, are handicapped both in the classroom and the clinic because of the lack of convenient and reliable methods for demonstrating the vibrations. Our teaching of physical diagnosis contains too many words which fail in the attempt to describe sounds heard in the chest. These words are apt to lack descriptive value in themselves and our further attempts at describing the sounds we hear too often demonstrate how far apart some of us are in our understanding of the more delicate meanings of words. This language difficulty is not only a problem in physical diagnosis, it is interesting that the same turbidity of speech occurs in the descriptions used in echo navigation where we find echoes referred to as "sighing," "grating," and "booming," according to the type of terrain reflecting the sound¹. In contrast, when such vibrations are converted into wave forms by a suitable recorder the differences in the vibrations become visually apparent and the results are accurately describable in terms of amplitude, frequency, harmonic and nonharmonic content, etc. Our attempts to demonstrate visual wave forms to the uninitiated have convinced us that it is not at all difficult to shift our usual method of thinking about vibrations to a visual wave form picture. By listening to chest sounds and seeing their wave forms it has been our experience that one becomes aware of finer distinctions in sounds and at the same time one realizes the superiority of visual analysis.

Various visual methods of sound recording have been used in physical diagnosis, including the early work with manometric flames and revolving mirrors, later the use of tambours and mirrors, and more recently stethoscopic pickups in conjunction with electric amplifiers and mirror-type tension galvanometers. Major's text on physical diagnosis records a few chest sounds using a cathode ray tube circuit². These methods have in general been technically difficult to operate or the apparatus has had frequency characteristics which restricted the value of the results obtained. Some of the component parts in the methods used in the past are still subjects of controversy, for example the filtering effect of rubber tubing, the lack of line-

* Received for publication August 19, 1941

A portion of the material presented in this article was exhibited at the Cleveland Meeting of the American Medical Association, and received an honorable mention.

From the Departments of Physiology and Medicine, University of Nebraska College of Medicine, Omaha, Nebraska

arity in the frequency response of diaphragms, the shapes of stethoscope bells and the air pockets enclosed. The inertia and restoring torques of galvanometers have affected the frequency characteristics of some of the equipment used. The range of uniform frequency response is surprisingly limited in some of the tension wire type of galvanometers. In spite of these handicaps useful and serviceable apparatus has been developed for the recording of heart tones although some of these devices filter out certain vibrations which might well be of clinical interest. From our experience the recent instrument developed by Kountz and associates³ and the one by Boone⁴ are advances in meeting the problem of fidelity of recording.

Many terms have been used to name the instruments designed for the recording of heart tones. Greater uniformity would be distinctly desirable from the standpoint of indexing. The term "stethograph" could well be used as the generic classification for apparatus which records sound waves and vibrations graphically. Our suggestion is that "electrostethograph" be retained as a subdivision, which should include stethographs in which vibrations are picked up by direct contact without involving tubing or air compartments, and in which the amplification and recording are purely by electrical means. The particular characteristics available in electron amplifiers and the cathode ray types of tubes are sufficiently distinctive to warrant this subdivision. The term "electrostethograph" was first proposed by Bierring, Bone and Lockhart⁵ but in the later development of their apparatus by Lockhart the term "stethograph" was used.⁶

METHOD

Recent developments in electronics permit the easy design of visual recording apparatus which will accurately record vibrations over wide frequency ranges. The uniform response of crystal type microphones permits the use of a compact microphone with an ample voltage output. We used the Shure 66 D type which has a contact face diameter of 0.75 inch and a mechanical connection between the contact button and the crystal making it sensitive to all contact vibrations but relatively insensitive to air-borne vibrations. This avoids the filtering problems due to rubber tubing, diaphragms, or stethoscope bell shapes. The frequency response is linear up to 1500 cycles per second but is reduced by 10 db at 2000 and 25 db at 8000 cycles. This frequency range is more than adequate for all sounds encountered in chest work.

The amplifier was resistance-coupled, single-ended and with a time constant of one second. With properly designed circuits and using a 3 inch cathode ray tube it was possible to assemble the complete apparatus, except for the cameras, in a small leatherette case with a total weight of less than 15 pounds. (Figure 1) In part of the work a filter condenser was inserted into the input circuit changing the time constant to about 0.2 second.

The cathode ray tube circuit was conventional, the short persistence type of tube being used because of the greater photogenic power of the blue end of the spectrum.⁷ A sweep circuit was included using a type 885 tube, and provisions were made for locking the sweep to the wave forms being stud-

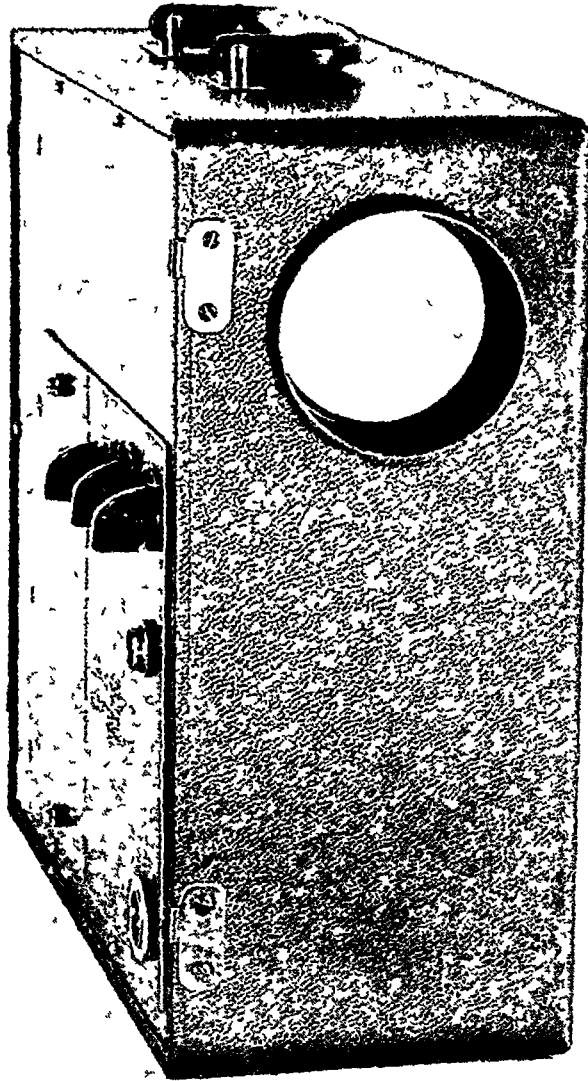


FIG 1 Electrostethograph The lid has been removed showing the various controls. The single exposure camera or the moving film camera is fastened by a bracket in front of the cathode ray tube.

ied. A bracket was mounted at the end of the case to hold the cameras. For single exposures (to be described later) a commercial 35 mm camera with an $f\ 3.5$ lens was used. For continuous film exposures the escapement mechanism was removed from an 8 mm movie camera, alternate teeth were

removed from the driving drum to permit the use of 16 mm film, and the lens was refocused. The governor was then readjusted. This gave a compact continuous film camera.

Although the equipment was constructed for the study of chest sounds of various types our particular interest here was in the question of transmission of lung sounds to the chest wall. A source of vibration was necessary and several were tried. We used ordinary percussion as a source of vibration, as well as several mechanical vibrators in which the amplitude and frequency were adjustable. Since this method involved a vibrator which varied in position on the chest wall and a microphone pickup, which was moved about the chest, relationships were complex. Transmission along the ribs was troublesome. It would have been an advantage, we think, if the percussor and the microphone were made into a single unit. The percussion blow would of course give a large deflection on the cathode ray screen but following this one would get the vibration response of the chest to the blow. Attempts to locate the percussing instrument at some fixed point on the chest wall which would be suitable for a study of the entire chest were not very successful.

We next tried transmitting the vibrations to the chest by means of a Jensen 8 inch speaker fitted with a funnel-shaped enclosure covering the diaphragm. Large heavy tubing was connected from the spout to the mouth of the subject. The speaker was operated at various frequencies and energy levels by a sine wave generator. The microphone was placed in contact with the chest wall and the transmitted wave forms studied. Variations in transmission and harmonic components were noted and the normal relations, to be described later, could be observed, but this method required too much cooperation on the part of the subject to be of practical clinical use.

The "loudspeaker" method did show some potentialities, however, which might make it of value in studying certain aspects of lung physiology. Since the source sound was produced electrically it was possible to apply this frequency from the sine wave generator to the horizontal plates on the cathode ray tube in place of the sweep circuit. Keeping the amplified vibrations picked up from the chest wall still connected to the vertical plates, the resultant figure seen on the tube is made up of the deflections laterally due to the source frequency while the vertical deflections are the source frequency as picked up after being transmitted through the chest. If the transmitted wave suffered no changes other than amplitude the resultant wave form would be a circle or an ellipse. The formation of harmonics would appear as waves superposed on the closed curve. Changes in the phase between the source and the picked-up wave appear as sloping of the elliptical patterns to right or left. These figures are known as Lissajous figures and are widely used in the study of distortions in amplifiers, frequency measure-

ments, etc [†] This method showed a marked increase in harmonic content in the wave forms occurring at the end of expiration as well as various phase shifts during inspiration depending in part upon the tenseness of the throat and shoulder muscles, and the way the subject controlled the mouth and muscles of the pharynx. The effect of frequency on wave form could also be observed.

The method finally adopted was to have the subject phonate at his natural frequency. In ordinary speech electrostethograms show that if a microphone is placed in contact on the neck at the side of the larynx the wave form observed comprises a "fundamental" frequency which is relatively constant with various overtones superposed on this fundamental. Fahr in his discussion of Martini and Mueller's studies on percussion and auscultation uses the term "fundamental" for the relatively constant frequency and "formative" for the overtone portions.⁷ If the subject says "A-h-h-h-hH" or "N1-1-1-1-Ne" the pattern, except for starting and stopping, is relatively constant, and the lowest frequency varies from about 90 to 200 cycles per second. Under these circumstances the wave form obtained would seem to approximate the carrier wave form as pointed out by Dudley in his discussion of the development of the Voder, an instrument for the artificial synthesis of speech.⁸ Such a natural frequency can be maintained easily by most individuals, and the wave forms picked up by the microphone at various parts of the chest wall are reproducible. In the same individual moderate variations in this fundamental or carrier wave frequency do not markedly change the wave shapes obtained. At high frequencies there is some simplification of the wave forms obtained and it is characteristic that chest wave forms are simpler in harmonic content in women than in men. If the subject phonates at a moderate intensity the variability due to variations in respiratory volume and to approaching expiration are not observed, in contrast to the loudspeaker method.

During the observations the subject should be in a comfortable and relaxed position. Tensing of the thoracic muscles can increase harmonic content and the results are not easily reproducible. Ambulatory patients sit on a short stool, somewhat roundshouldered in posture with the arms resting comfortably at the side. These details are the same as those used in percussion of the chest.

[†] Due to space limitation it is impossible to give any discussion of harmonic wave analysis. Numerous machines have been devised for analyzing harmonic wave forms and the mathematics of the more complex wave motions is highly technical. However, much useful information can be obtained from wave form studies without a knowledge of the mathematics of wave motion. *Sound Waves, Their Shapes and Speeds*, by D. C. Miller (Macmillan, 1937) gives an excellent and easily readable description of sound waves. The Radio Corporation of America Technical Bulletin TS-2 illustrates some of the Lissajous figures used in frequency determinations. *The Cathode-Ray Tube at Work* by John F. Rider, 1935, Chapter V, gives an elementary description of Lissajous figures and phase relationships. *Engineering Mathematics*, C. P. Steinmetz, McGraw-Hill Book Company, 1917, Chapter VI shows in a number of figures the effects of varying the amplitude of different harmonic components.

Having the subject phonate, the sweep circuit frequency is adjusted until the wave forms stand still. This occurs whenever the chest wave frequency is some multiple of the sweep frequency. Using the 3 inch cathode ray tube the sweep is adjusted so that four or five complete cycles appear on the screen. This spreads a cycle out to about 2 cm and is sufficient to make frequencies up to 1000 cycles per second easily visible. If higher frequencies are to be studied the sweep can be accelerated until only one cycle appears on the screen, giving a spread of about 3 inches. The amplitude of the chest wave forms is then adjusted by varying the gain control of the amplifier. Having the subject phonate each time, the microphone is moved to a new position while the examiner observes the wave form. Occasionally the subject will change his frequency sufficiently so that the waves do not remain stationary but move to right or left across the fluorescent screen. The apparatus is provided with a synchronization control or locking device which can be adjusted to keep the sweep and chest waves in synchronization over a considerable range. With some individuals no locking is necessary. If movement of the wave occurs then (1) the sweep frequency can be re-adjusted, (2) locking can be used, or (3) the subject can readjust his frequency a little. In the last situation on a few occasions we have connected an earphone to our sine wave generator and adjusting this to the subject's fundamental frequency, we have permitted him to hear this sound. He will then return to pitch. Before starting a series of observations we try to determine with a few trials the frequency the subject can maintain most easily. By engaging him in conversation, this fundamental frequency becomes apparent and if he tries to say "Ni-I-I-I-Ne" at a different frequency, we encourage him to say it more naturally.

Since by the phonation method the chest sounds are harmonic, i.e., uniformly periodic in character, it is possible to have them appear at the same position on the screen by the electrical means described. The appearance to the observer is that of a train of wave forms standing still during the phonation. Aside from permitting convenient visual observation it is also possible to photograph them with a snapshot camera. Using a standard 35 mm camera 36 exposures may be made on a single roll of film. The single exposure method results in marked film economy as compared to a method omitting the sweep and using continuous moving film. For example, to spread the wave forms out to one inch per cycle would require 90 inches film travel per second for a frequency of 90 cycles per second.

When studying phonation sounds the heartbeats of course appear on the fluorescent screen and are quite marked on the left side in front. Since the first and second heart tones are considerably lower in frequency the effect of the heart beat is to move the base line of the chest sound up and down. Since there are many chest waves to one heart beat, this movement does not interfere with adequate perception of the chest wave. The heart beats do not appear on the photograph. With excessively loud murmurs probably a

study of chest sounds in the region of the heart would require further apparatus considerations. So far we have not experienced this difficulty. When photographing the chest sounds the operator observes the wave form on the fluorescent screen and releases the shutter during the midportion of the phonation. We prefer a between-the-lens shutter on the camera because focal plane shutters, especially those that move in the same axis as the sweep, may miss the wave entirely.

A holder for the microphone is of great value and figure 2 illustrates a suitable type. This suspends the microphone in the middle of a band of

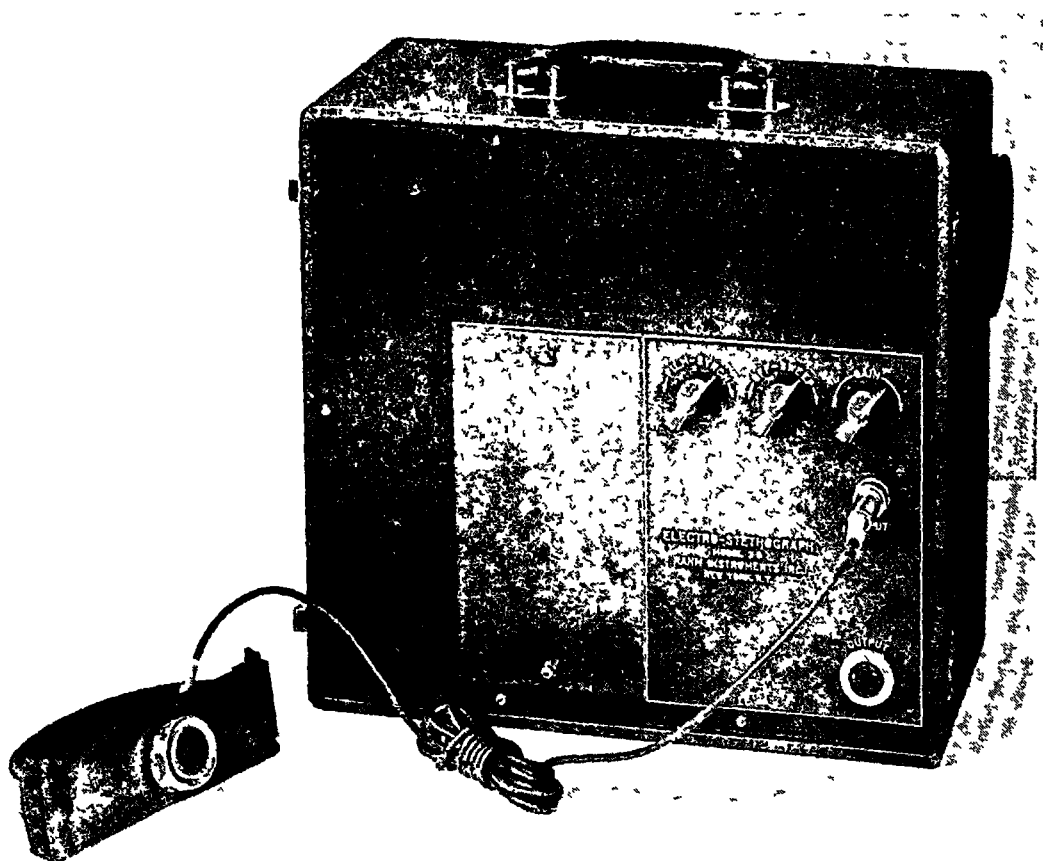


FIG 2 Holder for microphone, and side view of electrostethograph

rubber and thus separates the movements of the operator from the subject. At the same time the holder permits the microphone to move a little with the movements of the subject without slipping along the skin. The holder is placed usually so that it is parallel with the ribs and pressed firmly enough so that the end pieces are against the subject's chest. Static microphone pressure is not critical.

Excessive dryness of the throat will occasionally simplify the wave forms obtained. Excessive mucus in the pharynx as from postnasal catarrh may

at times interfere with reproducible results or produce phonchi. Clearing the throat and coughing will eliminate these. Since the amplitude of the wave forms is of interest it is advisable to place the microphone on alternate sides of the chest instead of making a series of observations on one side before studying the other side. This is particularly advisable when studying patients who are weak or who tire easily. Errors from this source have been eliminated in a more recent modification of the method described. That is, by the use of two microphones, double amplifier, and an electron switch it is possible to photograph or observe two chest sounds simultaneously on a single cathode ray tube. This makes more precise study possible but at the present time we have not used this method sufficiently to delimit its actual value.

The areas studied were located by external landmarks and the following system was adopted for location. The notation RP-T6-7 cm means a point on the right side posterior at the level of the sixth thoracic spine and 7 cm from the midline. In the back the level is referred to the spinous process. Distances are measured at right angles to the spine. In front we have followed the ribs laterally. Thus LA-T4-10 cm means a point on the left side, anterior, and 10 cm from the midline along the fourth rib. Various abbreviations have been used which are familiar such as "MCL" for mid-clavicular line, and "PAX" for posterior axillary line. The contact button of the Shure microphone is 0.75 inch in diameter so that it has not been necessary to make a distinction between ribs and interspaces. For more accurate vertical localization the symbol " $\overline{T4}$," i.e., with a bar above means the interspace below the fourth rib, while " $\underline{T4}$ " means the interspace above the fourth rib. This method of location has proved practical in use.

Although the film record can be studied directly it is convenient to transfer the wave forms to a 14 by 17 inch sheet of paper by using a light box and locating the wave forms in the approximate position on a body outline (Figure 3). Direct tracing with this size sheet avoids crowding and the wave forms can be traced quickly. In some cases where the chest was deformed the camera was used to photograph the body outline and this outline was enlarged and projected onto the sheet for the outline. The distortion of chest radiographs makes it undesirable to attempt to superimpose the wave forms onto a chest plate.

MATERIAL STUDIED

Electrostethographic studies were made on 10 normal subjects and 22 patients from the University Hospital and Dispensary. In all about 1500 photographs were made. The cases were studied by the Medical Department and in addition were reexamined by one of us. Roentgenograms were made in all cases within 24 hours of the time the electrostethographic studies were made.

DISCUSSION

Figure 3 illustrates the types of wave forms observed in a normal male, and figure 4 is a grouping of wave forms from different chest areas in five normal males. In the upper chest the wave form comprises the fundamental frequency and an extra wave midway between. This is apparently an octave or first harmonic. The amplitude of the wave form is usually greater at the right apex than the left. Going down the back there is a progressive disappearance of this harmonic and at the bases of the lungs the wave form is a sine wave. The lower borders of the lung can be defined sharply by the sudden reduction in amplitude. Behind the heart on the left

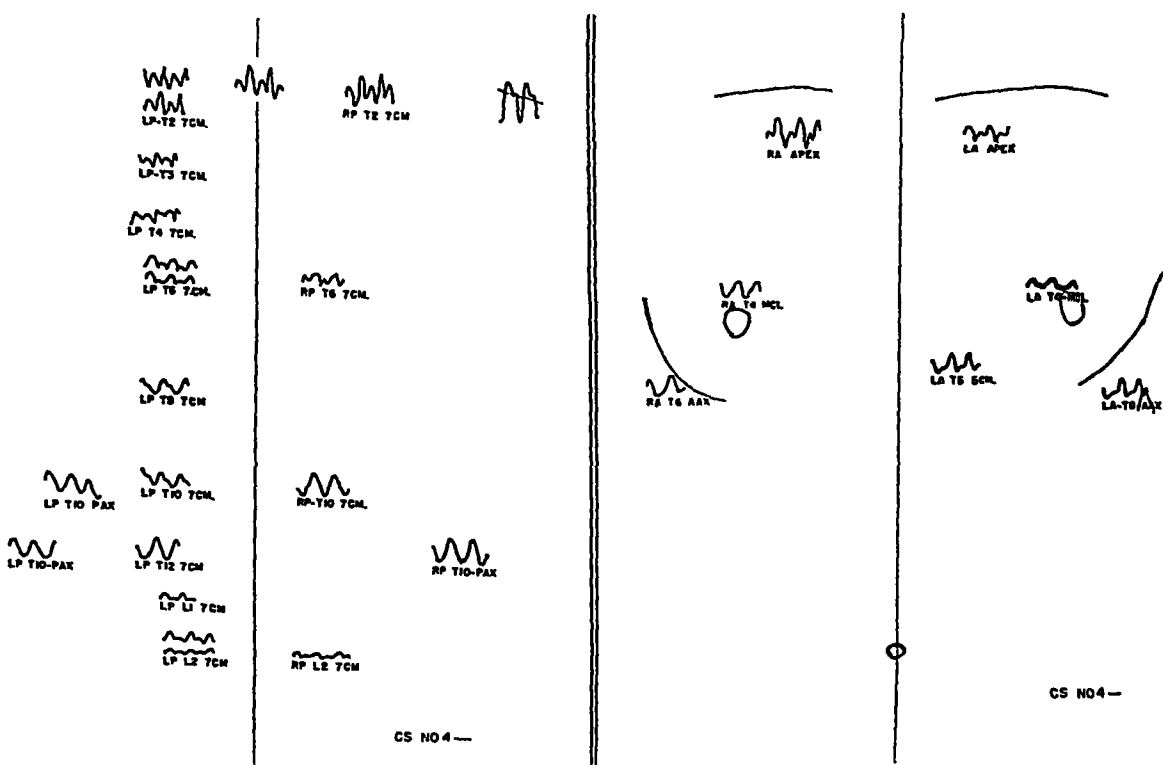


FIG 3 Wave forms observed in a normal chest by the phonation method

side there are characteristically remnants of harmonics present which are not present at the symmetric point on the right side in the normal. Occasionally, in the normal, higher harmonics are seen at the apices and these are more commonly on the right than the left. If the subject phonates loudly and harshly these may be conspicuous. Transmission of harmonics extends further down over the spinous processes than it does laterally to the spinal column. If the microphone settings are made 5 to 7 cm lateral to the spinal column there will be more harmonic components on the left back than the right. Farther laterally, the wave forms are essentially similar except for the heart area previously noted.

In front there is excessive transmission of harmonics in the upper portion of the sternum The wave form in the area of the heart in front is variable In some cases there is a sharp reduction in amplitude, in others there is a marked change in the harmonic content, while in others there is little change until one is well into the superficial cardiac dullness

In pneumothorax CS 28 an injection of 300 c c air reduced the amplitude at the posterior apex on the injected side 70 per cent as compared with a

	CS-5	CS-29	CS-3	CS-4	CS-12
RP-T2-5CM					
LP-T2-5CM					
RP-T7-5-7CM					
LP-T7-5-7CM					
RP-T9-5CM					
LP-T9-5CM					
RP-T11-PAX					
LP-T11-PAX					
RP-L2-5CM					
LP-L2-5CM					

FIG 4 Grouping of wave forms in five normal males to indicate the types of variations observed

difference of only 10 per cent before injection (Figure 5) At LP-T3-5 cm the reduction was 75 per cent, at T5-5 cm , 78 per cent, and at T7, 70 per cent At LP-T5 posterior axillary line the reduction was 70 per cent as compared with symmetric points on the opposite side Our experience would indicate that in the absence of adhesions there is a simple loss in amplitude With adhesions there can be a marked increase in amplitude and persistence or alteration of harmonic components, with the appearance of abnormal wave forms, i e waves not seen in any area of the normal chest

Hydrothorax when uncomplicated by adhesions results in a loss of transmission as shown in CS 32 (Figures 6 and 7) Radiologically, at the time of the first electrostethograms the left chest was almost entirely opaque. Reductions in amplitude amounted to as much as 90 per cent. Later, when the radiological appearance showed the upper third or half to be partly cleared, the differences in amplitude compared with the normal side, amount to 40 to 50 per cent. There was no evidence of adhesions in this case and the fluid was an inflammatory non-tuberculous exudate with a specific gravity of 1.018. However, aside from the reduction in amplitude on the hydrothorax side many of the wave forms were abnormal in harmonic content.

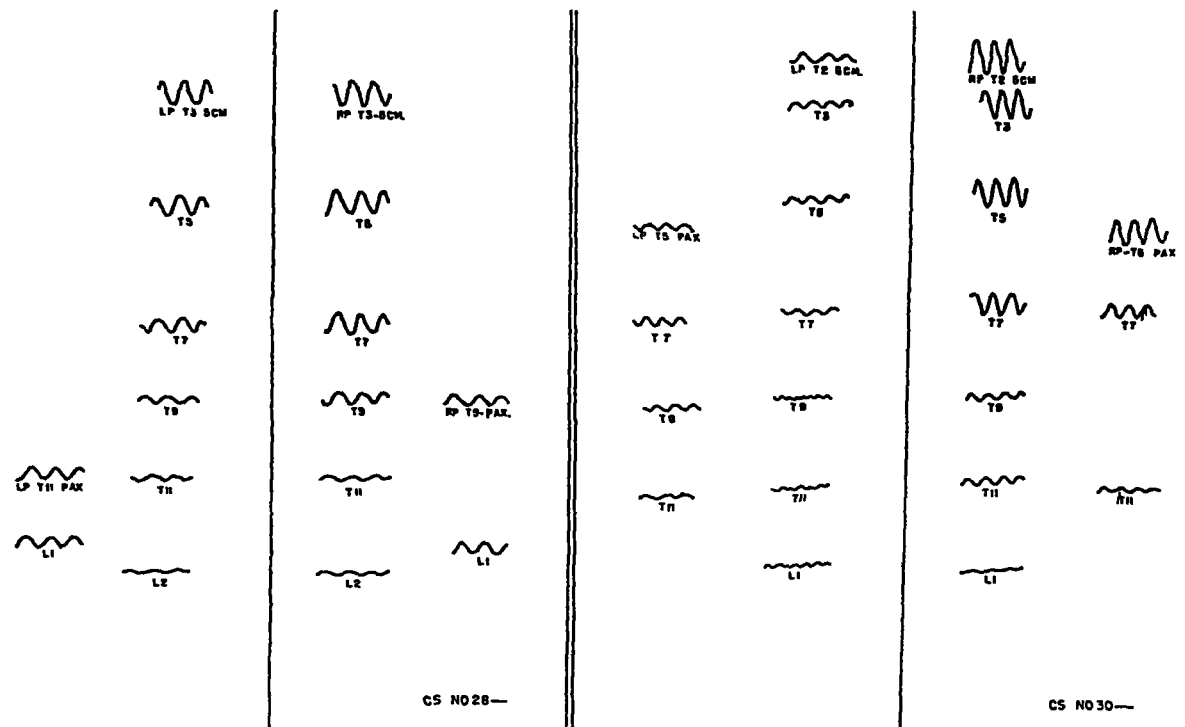


FIG 5 Case CS 28, pneumothorax. Left chart is wave forms observed over back before injection of 300 c c air. Right chart is after injection.

CS 24, with fluid at the right base, showed numerous abnormal wave forms (Figures 8 and 9). After withdrawal of 1500 c c of transudate the wave forms were still markedly abnormal but there were alterations in the wave form corresponding to the radiological evidence of lowering of the fluid level. These consisted of phase reversals and changes in harmonic amplitudes. After removal of a portion of the fluid the roentgen-ray showed a dense adhesion which autopsy later revealed as dividing the pleural space into a lower and an upper cavity. The interpretation of the complex wave forms obtained at the right base in CS 24 is obscure at present but in comparison with the normal then abnormality is grossly apparent.

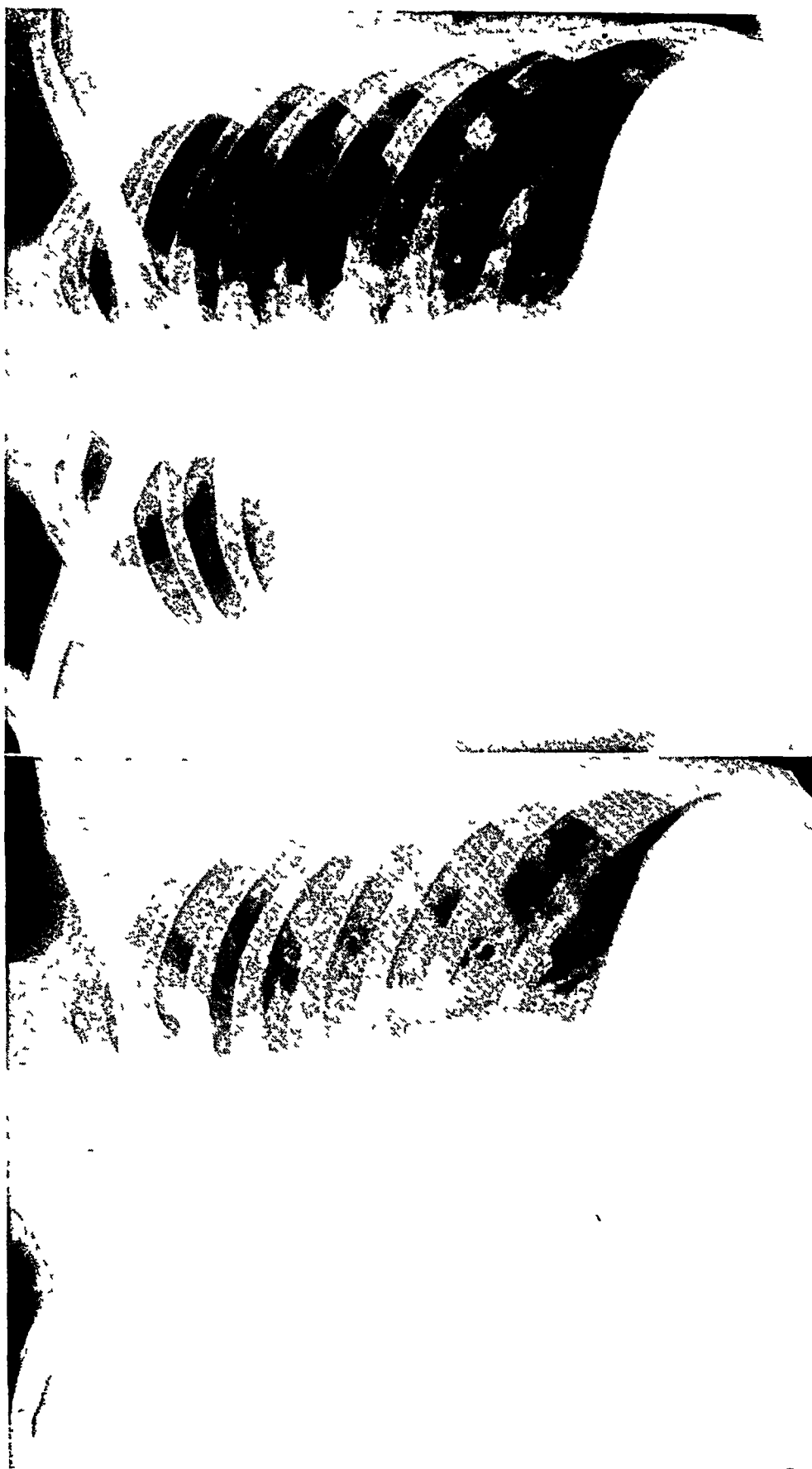


FIG 6 Case CS 32, pleurisy with effusion Radiographs (left) at time of first studies, and right at time of second studies

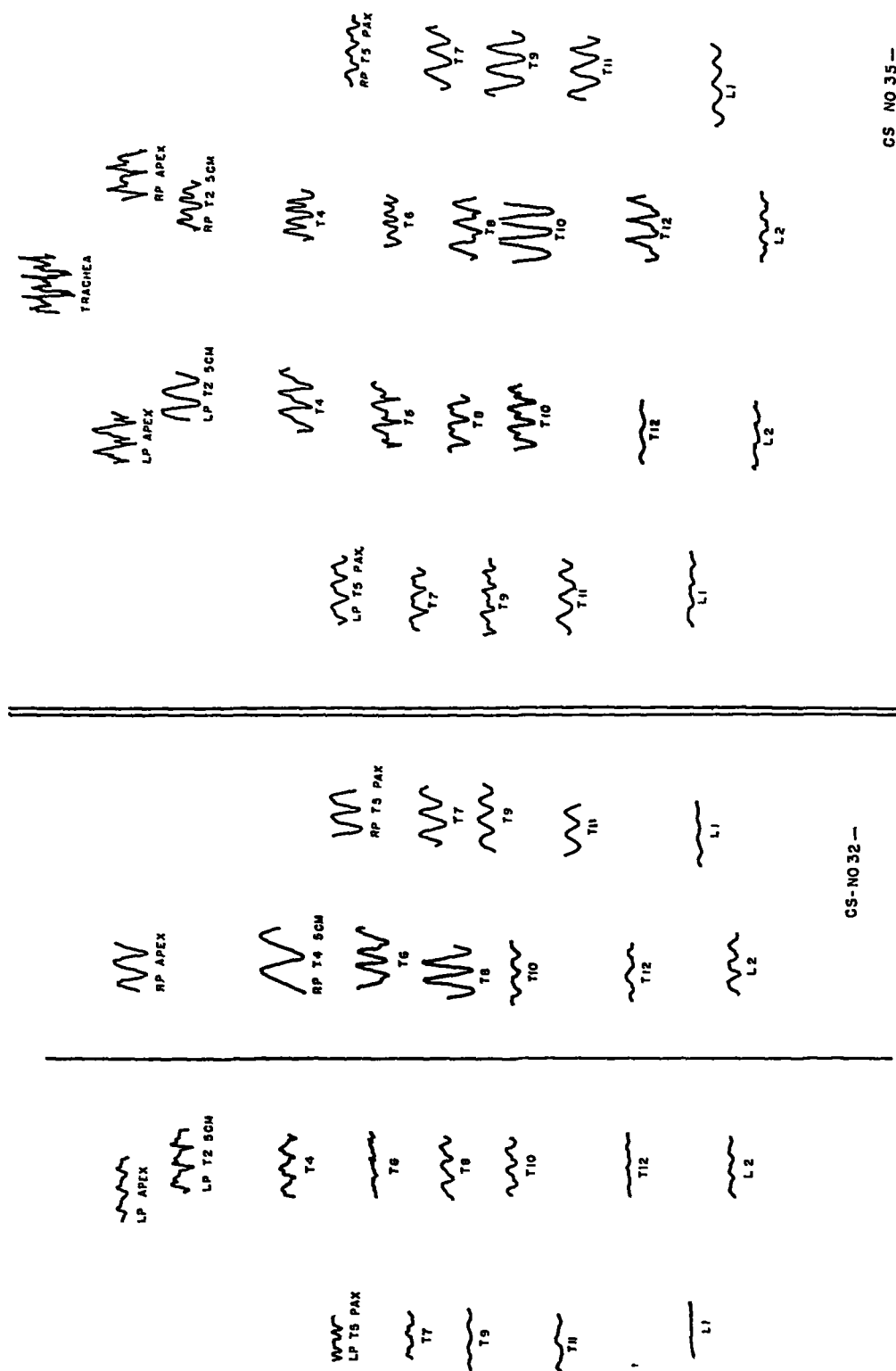


FIG 7 Electrosthethographs observed in case CS 32 (figure 6)

Both case CS 24 and 32 showed abnormal waves on the normal side of the chest. In CS 24 there was a marked increase in the size of the heart with some shift to the left but in CS 32 the roentgenogram was normal. The abnormalities consisted of (1) harmonic transmission in areas in which it is normally absent, (2) unusual variations in amplitude, and (3) the occasional appearance of large amplitude sine waves. These large amplitude waves also occurred in radiologically normal lung in CS 21, a man with a carcinoma of the lower half of the left lung. We have observed them elsewhere and wondered whether they might not be an expression of regional emphysema.

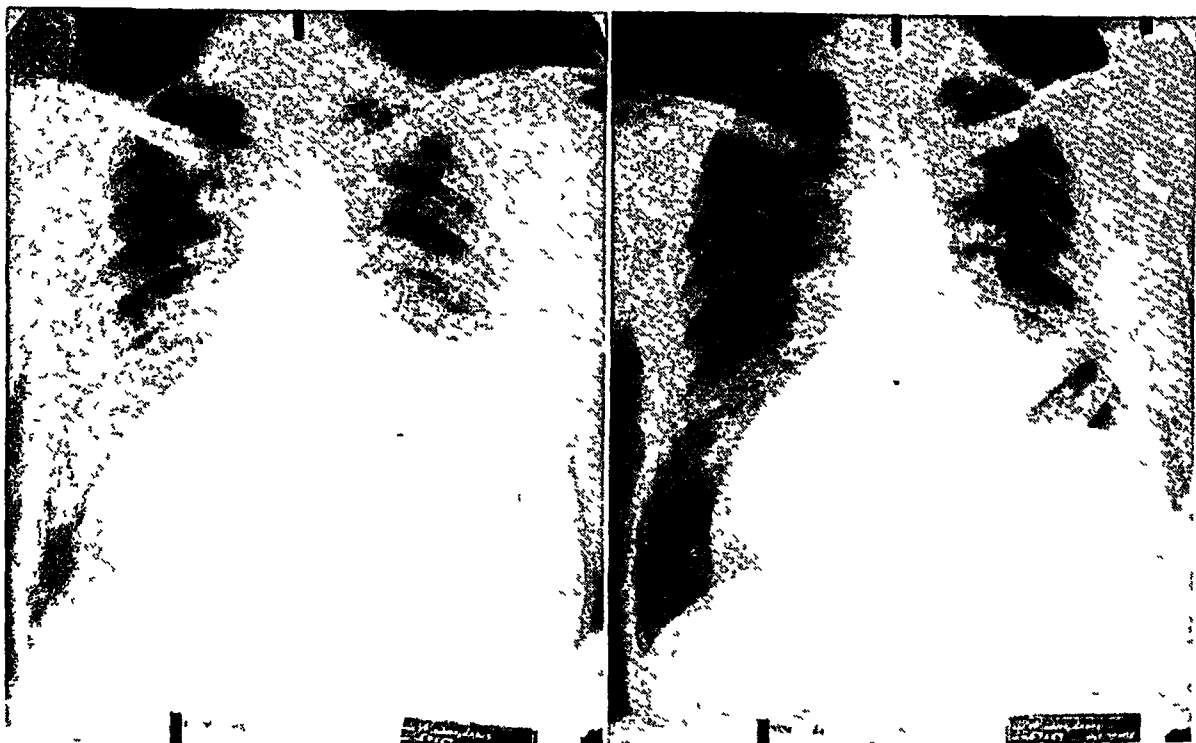


FIG 8 Case CS 24, radiographs before (left) and after (right) thoracentesis in a case of right hydrothorax with chronic myocardial failure

Cases CS 6 and CS 21 were studied because of healed fibrotic apical lesions. Case CS 6 showed a marked transmission of multiple harmonics to the apical area. He had a well-marked tracheal deviation from fibrotic contracture. Case CS 21 had an apical fibrosis confined to the apical tip without tracheal deviation. The amplitude was increased 300 per cent in the supraclavicular area as compared with the normal side. The subclavicular electrostethograms were essentially the same on the two sides.

Two cases of disseminated lesions showed abnormal harmonic components scattered throughout most of the chests. Case CS 23 was proved to be miliary tuberculosis at autopsy while CS 26 was identified as actinomycosis originating in the jaw. Our studies in pneumonia have been in-



Fig 9 Case CS 24, electrocardiograms before (left) and after (right) thoracentesis. Note the marked abnormality of the wave forms and the inversion of the flat-topped waves after removal of fluid.

decisive because of current therapy and the lack of adequate radiographic study. We have not been able to study lobal consolidation although Wheeler using our equipment has observed increased amplitude and harmonic transmission.⁸

As noted before, the tenseness of the muscles affects the wave form somewhat, increasing the harmonic content. The amount of excess fat does not appear to be a handicap. In Case CS 34 after a radical amputation of the left breast six years previously, the wave forms did not appear to be materially altered although there was some increase in amplitude on the amputated side.

We have not yet been able to study the effect of diffuse pulmonary or peribronchial fibrosis unless it appeared as a complicating factor from chronic heart failure in case CS 24.

In our discussion we have interpreted the wave forms observed in terms of transmission of sounds from a source comprising those factors involved in voice production. When one compares the electrostethogram obtained at the side of the larynx with those obtained in the chest, the losses in transmission are readily apparent. However, when one encounters some of the complex wave forms observed in the lower parts of the chest in cases of empyema with carcinoma, in bronchopleural fistulae, and in old empyemas, etc., it seems necessary to consider the possibility that some of the harmonic components are formed by reverberation or echo phenomena either in air spaces or in tissues capable of acting as vibrating masses.

Martini and Mueller reported in 1923 the "free periods" of vibration of air in portions of the bronchial tree.⁷ These periods of "free vibration" were determined in freshly isolated lungs using a mirror tambour method and at low energy levels in their studies on bronchovesicular breathing. We have not studied the frequency of the breath sounds at different areas of the chest although it is readily observable by increasing the gain of the amplifier. The frequency can be estimated visually but photographic records would of course require a moving film camera. The resonating frequencies may be distinctly different at the relatively high energy levels obtaining during phonation and the normal blood supply in the normal lung tissue may well alter the frequency relationships observed by Martini and Mueller. With the equipment available today their work should be repeated. If the frequencies determined by Martini and Mueller are approximately correct for intact lung (and Fahr's clinical observations would imply this), then from our observations we doubt whether the "free vibration" contributes materially to the electrostethograph record in the normal by the phonation method. However, in the presence of hydrothorax or adhesions, or the conglomerate types of masses occurring in carcinoma, bronchial abscesses, etc., the marked abnormality of wave form already observed by us, including in particular the flat-topped waves, may well be due in part to multiple vibrating systems operating at forced resonance levels. This would be anal-

ogous to the square wave formation observed in overloaded vacuum tube circuits, the wave form being produced by excessively rich harmonic oscillations

SUMMARY

1 An electrostethograph has been described utilizing a crystal microphone with mechanical contact, an electron amplifier and cathode ray tube recorder with a wide and uniform frequency response. By application of various improvements in design the apparatus except for cameras can be enclosed in a small case weighing less than 15 pounds.

2 Utilizing phonation and a sweep circuit the method permits visual study of chest sounds as well as single photographic exposures.

3 In the normal the characteristic wave forms observed in the upper chest comprise a fundamental frequency and an harmonic. These undergo progressive changes becoming sine waves at the lower border of the lungs. The lung borders can be accurately outlined. Behind the heart on the left the wave forms show differences as compared with the symmetric area on the right.

4 Changes in wave forms observed in a few pulmonary diseases have been described.

5 The phonation method described offers definite refinements in the study of chest sounds. Simplicity of operation and compactness make the method a practical one for the study of clinical patients.

We wish to express our appreciation to Drs H. B. Hunt and J. P. Tollman and the Radiological Department of the University of Nebraska College of Medicine for assistance in correlation and for space, and to Rahm Instruments, Incorporated, 12 West Broadway, New York City, for technical aid in the design of the apparatus used.

BIBLIOGRAPHY

- 1 WRIGHT, LAWTON Floating bridges, Saturday Evening Post, April 5, 1941, page 22
- 2 WALKER, G., in MAJOR, R. H. Physical diagnosis, 1938, W. B. Saunders Co., Chap. V
- 3 KOUNTZ, W. B., GIBSON, A. S., and SMITH, J. R. The use of the cathode ray for recording heart sounds and vibrations. 1. Studies on the normal heart, Am Heart Jr, 1940, xx, 667-676
- 4 BOONE, B. R. An amplifier for recording heart sounds through the use of the cathode ray tube, Jr Lab and Clin Med, 1939, xxv, 188-193
- 5 BIERRING, W. L., BONE, H. C., and LOCKHART, M. L. Use of the electrostethograph for recording heart sounds, Jr Am Med Assoc, 1935, civ, 628
- 6 LOCKHART, M. L. The stethograph, Am Heart Jr, 1938, xvi, 72-78
- 7 FAHR, G. The acoustics of the bronchial breath sounds. Application of phenomena of auscultation as heard in lobar pneumonia, Arch Int Med, 1927, xxix, 286-302
- 8 WHEELER, W. L., JR. Personal communication
- 9 DUDLEY, H. The carrier nature of speech, Bell System Tech Jr, 1940, xix, 495-515

LIVER FUNCTION IN MENSTRUATION *

By ROBERT HEILIG, M D , and N L KANTIENGAR, B Sc , M B B S ,
Medical College, University of Mysore, Mysore, South India

WHILE studying the excretion of hippuric acid in pregnancy Hirsheimer (1935) has shown that elimination of hippuric acid after administration of sodium benzoate is diminished towards the termination of normal and toxemic pregnancies, results confirmed later by other authors. The present investigation was undertaken to find whether the hepatic function during the menstrual period varies consistently from that recorded in the interval.

For this purpose we used Quick's test, based on the ability of the liver to detoxify benzoic acid by conjugation with glycine to form hippuric acid. First devised by Quick (1931), this test has been used sufficiently to give a fairly good idea of its value. The method is simple and consists of a gravimetric determination of the total hippuric acid in the urine for four hours after the oral administration of a dose of sodium benzoate. According to Snell (1935), this test gives reliable information as to the degree of hepatic damage present as shown by his studies at operation and necropsy. The test measures the amount of hepatic tissue able to build glycine, the amount of glycine available for conjugation with benzoic acid determines the quantity of hippuric acid eliminated in the urine. The less the liver tissue participates in glycine production the less can hippuric acid be synthesized.

Quick (1936) has worked out normal variations in the hepatic efficiency in men, the values range from 80 to 120 per cent. Pathological variations have also been studied by him especially in jaundice, cirrhosis, hepatitis and cancer, many papers have been published since, confirming Quick's investigations and applying them to different clinical purposes. Our attempt to ascertain whether variations of hepatic function occur during the menstrual period was executed in the following way.

EXPERIMENTAL

The subjects selected were 17 healthy women, students of the Mysore University Medical College and some staff members of the Krishnarajendra Hospital, all having normal menstrual history. Their ages varied from 19 to 35 years, the majority being from 22 to 24 years of age. All the subjects were subjected to the Quick liver efficiency test on two occasions, one being on the thirteenth to fourteenth day of the menstrual cycle, the other within 8 to 16 hours after the onset of menstruation.

* Received for publication June 2, 1941

METHOD

For 24 hours previous to the test, the subjects were asked to avoid excessive consumption of vegetables, fruits, drinks, and to abstain from any tonics or drugs. On the subsequent morning at 6 o'clock the subjects were allowed a light breakfast consisting of a small cup of plain milk and two pieces of toast without butter. One hour after the light breakfast, 6 grams of sodium benzoate dissolved in 30 c c of distilled water were given, this was im-

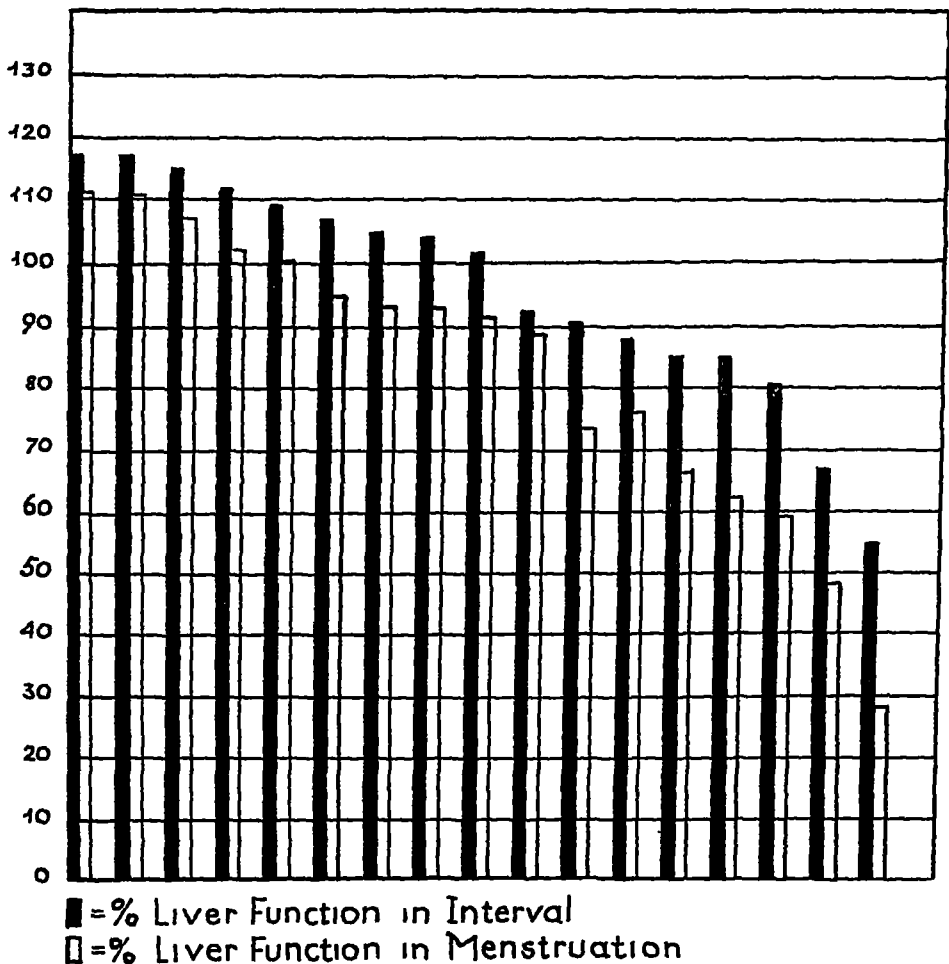


FIG 1 This figure gives a comparative idea of the efficiency of the liver both at the interval and on the first day of the menstruation

mediately followed by a drink of 120 to 150 c c of water. Immediately before taking the drug, the bladder was emptied completely and then complete specimens of urine were collected hourly for four continuous hours. Until the last sample of urine was collected the subjects were rested on a chair, and allowed to spend their time in reading light literature, as they complained of giddiness and weakness if they moved about, particularly when

the test was made on the first day of menstruation The hourly samples were pooled, and half the total volume was taken for estimation immediately, the other half being reserved for a duplicate experiment to check the results The sample of urine was acidified with 1 to 2 c c of dilute acetic acid, and

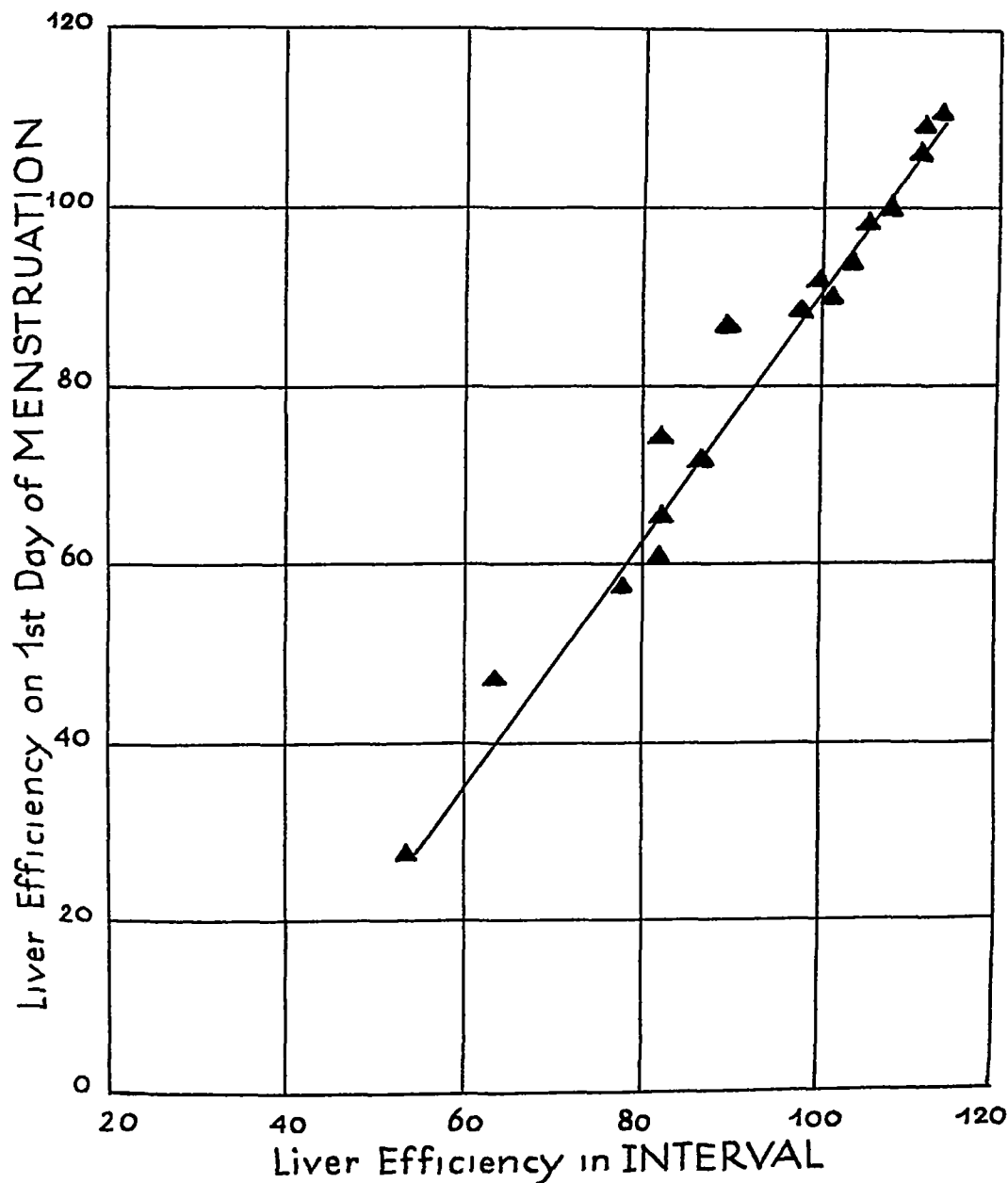


FIG 2 The function of the liver on the first day of menstruation and during the interval From the graph (figure 2) it can be seen that by studying the function of the liver, either at the interval or on the first day of menstruation, the function of the liver at the other period could be read with a variation of 2 to 3 per cent

concentrated on an electric boiling water bath until the final volume was reduced to 20 to 25 c c The concentrated urine was well cooled and acidified with 1 to 2 c c of concentrated hydrochloric acid until the sample gave an acid

reaction to congo-red paper Hippuric acid was allowed to crystallize out at the laboratory temperature The crystalline hippuric acid was collected on a fluted filter paper and washed frequently with a small quantity of cold water

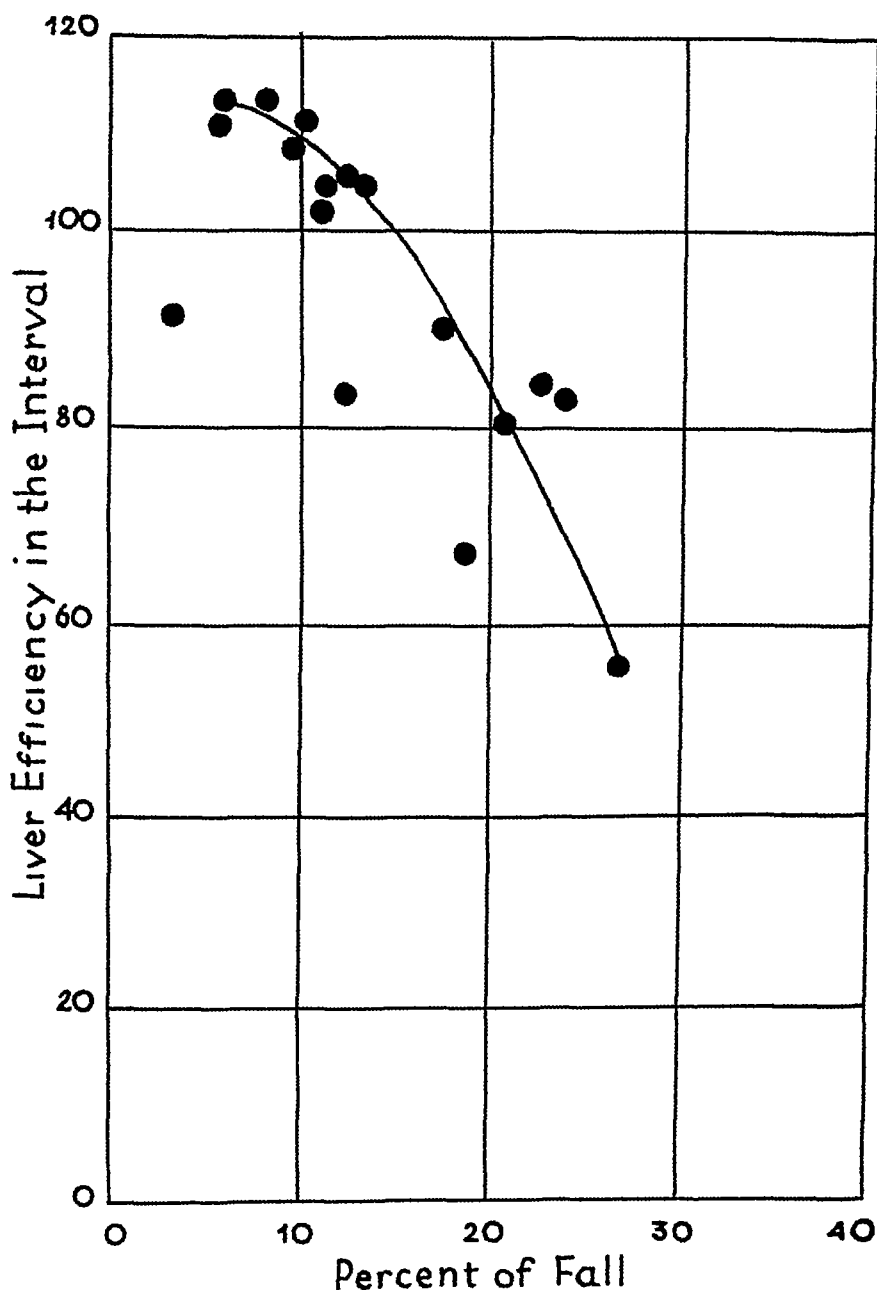


FIG 3 The percentage of fall in the efficiency of the liver From the curve it is seen that the percentage of fall was greatest in cases where the original function of the liver was at the lowest level

The total volume of the filtrate was measured in order to apply the solubility correction of 0.33 gram per 100 c c of the filtrate at 25°C to 26°C The crystalline hippuric acid was dried in an oven at 70 to 75°C and weighed

to constant weight. In cases where the urine was contaminated with menstrual blood, hippuric acid was recrystallized from alcohol and weighed. In a few cases the melting point of the samples obtained was determined to test the purity of the sample, the melting point varied from 184–186° C. In a few cases estimations were made with hourly samples to study the rate of elimination of the hippuric acid. To express the results in terms of benzoic acid, the figure for the weight of the hippuric acid obtained was multiplied by the factor 0.68. According to Quick, a normal adult will excrete 3 grams of benzoic acid in the form of hippuric acid in four hours, the normal range varying from 80 to 120 per cent of this amount.

To eliminate disease of the kidney and hypertension, which may affect the result, the blood pressure was recorded, and an examination of the urine was made in all the cases.

The accompanying table (table 1) gives the result of the efficiency of hepatic function in women, both at the interval and on the first day of menstruation.

RESULTS

The mean average of liver efficiency in the cases recorded was 95.72 per cent with a maximum of 117 per cent and a minimum of 56 per cent in the interval. From the results obtained, it could be seen that the function of the liver was lowered in the menstrual period compared with that recorded in the interval. The fall was nearly constant in subjects whose liver efficiency in the interval ranged from 95 per cent to 110 per cent. The variation in hepatic function was very small in cases where the liver function in the interval was over 110 per cent. A marked fall was observed in cases where the liver function at the interval was less than 90 per cent; the degree of fall depending upon the original liver function, the lower the function of the liver in the interval, the greater is the fall during menstruation.

In one case (case 5), the liver efficiency on the first day of menstruation was as low as 28 per cent which may be pathological. The clinical examination of the subject showed no signs of impaired health, especially no symptom of liver, kidney, heart or lung disease, or of diarrhea. The amount of hippuric acid collected in the third and fourth hour was 0.94 gm. According to Hirsheimer it is interpreted as normal when the output for one hour is found to be 0.90 gram or more, and such interpretation is necessary by the possibility of delayed absorption of sodium benzoate, though assimilation is usually rapid.

DISCUSSION

Our investigations prove beyond doubt that the liver function estimated by Quick's test is substantially impaired on the first day of menstruation. In the literature given in the Quarterly Cumulative Index Medicus 1931 to 1940, no references to examinations of the influence of the menstrual cycle on the

TABLE I

Serial No	Name	Age	Diet	Blood Pressure	Pulse Rate	Pulse Pressure	Interval		First Day of Menstruation		Percentage of F-all	Amount of F-all %	Urine Exam	General Remarks
							Hippuric Acid gm	Liver Efficiency %	Hippuric Acid gm	Liver Efficiency %				
1	H	35	M*	125/80	86	45	4.641	105.30	4.06	92.25	12.39	13.05	Nothing abnormal	European
2	K	24	V†	122/80	84	42	3.95	89.50	3.20	72.68	18.79	16.82	-Do-	Hindu
3	Mb	22	V	115/65	108	50	4.81	109.00	4.41	100.00	8.56	9.00	-Do-	Hindu
4	Mh	20	M	130/80	116	50	4.73	107.20	4.20	95.20	11.19	12.00	-Do-	Mohammedan
5	St	20	V	104/74	72	30	2.43	55.08	1.25	28.44	47.28	26.64	-Do-	Hindu
6	L	22	V	115/70	70	45	2.91	66.00	2.13	48.42	26.64	17.58	-Do-	Hindu
7	G	22	V	117/82	76	35	4.54	101.00	4.34	90.66	10.21	10.34	-Do-	Hindu
8	Sch	30	M	—	—	—	5.16	116.96	4.92	111.52	4.65	5.44	-Do-	European
9	V	20	M	100/70	76	30	4.05	91.80	3.93	89.08	2.96	2.72	-Do-	Indian
10	SS	24	V	—	—	—	5.16	116.96	4.91	111.06	5.0	5.90	-Do-	Christian
11	Rb	21	M	108/70	95	38	4.59	104.04	4.10	92.96	10.65	11.08	-Do-	Hindu
12	Sn	19	M	116/75	92	41	3.52	79.89	2.60	59.00	26.15	20.89	-Do-	Hindu
13	Sb	21	V	124/76	90	48	3.76	85.23	2.73	62.00	27.26	23.23	-Do-	Hindu
14	Rm	24	M	—	—	—	4.94	111.97	4.49	101.77	11.47	10.20	-Do-	Hindu
15	Abai	26	V	—	—	—	5.08	115.15	4.72	107.20	7.42	7.95	-Do-	Hindu
16	VK	24	V	—	—	—	3.75	85.00	3.30	75.00	12.00	10.00	-Do-	Hindu
17	Kbai	27	M	—	—	—	3.85	87.27	2.96	67.00	25.30	20.27	-Do-	Hindu

* M = Mixed food

† V = Vegetarian food

liver function were found. But there are other ways to show that our results are in accord with the facts established about physiological changes connected with menstruation. H. Kustner and Heilig have proved that the carbohydrate metabolism is deeply influenced by menstruation, results confirmed later by Eufinger. Heilig has shown that 100 grams of dextrose given orally on an empty stomach increase the blood sugar far more during the first two days of menstruation than in the interval, as the hypoglycemia following the alimentary hyperglycemia is well expressed also during menstruation, the abnormal high blood sugar values are most probably not due to pancreatic insufficiency. Srikantha et al. found definitely higher fasting blood sugar during menstruation than in the interval. Heilig suggested a reduced glycogen fixation in the liver as an explanation of these facts. It is further known (Heilig, 1924), that the water and chloride elimination is reduced up to 50 per cent during menstruation, compared with the elimination in the interval by the same healthy test persons, results being confirmed by Eufinger and Spiegler and by Thorn et al. and reproduced by injecting ovarian hormones (Thorn and Emerson). The fundamental investigations of the Viennese pharmacologist E. P. Pick (Molitor and Pick and Mauthner and Pick), confirmed clinically by Adlersberg and Minibek, leave no doubt that the liver is one of the main regulators of water-chloride elimination. As no sign of primary kidney damage due to menstruation is known, Heilig suspected the liver of being responsible for water-chloride retention in menstruation. As normal liver function is essential for sufficient glycine synthesis, which also is the condition for normal Quick test, glycine being required to transform the benzoate to hippuric acid, the facts mentioned before make it probable that the diminished hippuric acid output on the first day of menstruation is due directly to a diminished liver function. The question arises whether also extra-hepatic factors may influence the hippuric acid elimination.

As menstruation is due to, and is accompanied by a profound change in endocrine correlations, it is most probable that our results are a further clue to hormonal regulations of this partial liver function. Bartels and Perkin and Boyce and Fetridge proved by Quick's test that hippuric acid elimination is impaired in hyperthyroidism. We do not know whether the thyroid function varies regularly with the menstrual cycle, though clinical experience and experimental facts seem to make it probable (Sherwood). We intend to investigate this question and further to see whether Oestrone or Progesterone has a measurable influence on the results of Quick's test.

Further it is well known that the tone of the autonomic nervous system or the balance between the cholinergic and adrenergic systems is distinctly changed in menstruation in the sense of a cholinergic preponderance due to an increased choline content of the blood in the first days of the menstrual cycle (Sieburg and Patzschke). Harpuder has proved, partly in confirmation of previous investigations, that adrenalin increases, ergotamine—the sympathetic depressor—diminishes substantially hippuric acid elimination, sympathetic

depression means automatic stimulation of the cholinergic branch, menstruation, being accompanied by hypercholinemia, shows among other signs of "vagus stimulation," also diminished hippuric acid elimination. Whether the liver function is influenced by choline directly or by a change in the ionic balance is not known. As a last possibility that factors other than the liver may influence our results, we have to mention the part that the kidney plays in hippuric acid synthesis (Snapper and Gunbaum, 1935). We see no practical way to decide whether this "non-excretory" kidney function suffers in menstruation, but it seems most improbable that such differences between interval and menstruation, as shown in our figures could be due to an impaired renal benzoic acid-glycine conjugation.

Far from underestimating the liver specificity of Quick's test—supposing the kidney function to be normal—we believe that apart from a primary depressed glycine synthesis, influences of the autonomic nervous system and probably endocrine factors have to be considered in explaining our results.

SUMMARY

Quick's test was used to compare the liver function of 17 healthy women on the first day of menstruation with that in the interval.

Different possibilities are discussed to explain the impaired liver function in menstruation.

We wish to record here our thanks to the women students of the Mysore University Medical College and the Staff of the Krishnarajendra Hospital, Mysore, who offered themselves as subjects for experimental work, without whose willing cooperation this investigation would not have been possible.

Our sincere thanks are especially due to Dr C. Srikantha, B.A., D.Sc., Professor of Chemistry, Medical College, Mysore, for his kindness in giving us the laboratory facilities and sparing one of his assistants (Mr N. L. Kantiengar) for carrying out this investigation.

BIBLIOGRAPHY

- 1 ADLERSBERG, D., and MINIBECK, H. Zur Auswertung der Leberfunktionsproben im Tierversuch (Galaktoseprobe, Wasserversuch, Hippursäuresynthese bei der Phosphor und Tetrachlorkohlenstoffvergiftung), *Ztschr f d ges exper Med*, 1936, xcvi, 185-200.
- 2 BARTELS, E. C., and PERKIN, H. J. Liver function in hyperthyroidism as determined by hippuric acid test, *New England Jr Med*, 1937, ccxvi, 1051-1060.
- 3 BOYCE, F. F., and MCFETRIDGE, E. M. Studies of hepatic function by quick hippuric acid test, thyroid disease, *Arch Surg*, 1938, xcvii, 427-442.
- 4 EUFINGER, H., and SPIGLER, R. Der Einfluss des mensuellen Zyklus auf den Wasserstoffwechsel, *Arch f Gynak*, 1928, cxxxv, 223-231.
- 5 HARPUDE, K. Pharmakologische Beeinflussung des Purinstoffwechsels beim Menschen, *Ztschr f d ges exper Med*, 1924, xli, 1.
- 6 HEILIG, R. Menstruationsstudien I, *Klin Wchnschr*, 1924, iii, 576.
- 7 HEILIG, R. Menstruationsstudien II. Wasser- und Kochsalzhaushalt, *Klin Wchnschr*, 1924, iii, 1117-1119.
- 8 HIRSHEIMER, A. Synthesis and excretion of hippuric acid in pregnancy, *Am Jr Obst and Gynec*, 1935, xxix, 395-405.
- 9 KUSTNER, H. Bedeutung der Funktionen der weiblichen Genitalorgane für den renalen Diabetes, *Arch f Gynak*, 1922, cxvii, 158.

- 10 MAUTHNER, H, and PICK, E P Über die durch Schockgifte erzeugten Zirkulationsstörungen II Das Verhalten der überlebenden Leber, *Biochem Ztschr*, 1922, cxxvii, 72-93
- 11 MOLITOR, H, and PICK, E P Zur Kenntnis der Diuresehemmung durch Hypophyssenpräparate, *Klin Wchnsch*, 1923, ii, 2242
- 12 QUICK, A J Conjugation of benzoic acid in man, *Jr Biol Chem*, 1931, xcii, 65-85
- 13 QUICK, A J Effect of exercise on the excretion of uric acid, with note on influence of benzoic acid on uric acid elimination in liver diseases, *Jr Biol Chem*, 1935, cx, 107-112
- 14 SIEBURG, ERNST, and PATZSCHKE, WALTER Menstruation und Cholinstoffwechsel, *Ztschr f d ges exper Med*, 1923, xxvii, 324
- 15 SNAPPER, I, and GRUNBAUM, A The non-excretory functions of the kidney, *Proc Staff Meet Mayo Clin*, 1927, ii, 300
- 16 SNELL, A M New tests of hepatic function, *Collected papers of the Mayo Clinic*, 1935, xxvii, 106-108
- 17 SHERWOOD, T C Further studies on ovarian-thyroid relationship, *Endocrinology*, 1940, xxvii, 925-928
- 18 SRIKANTIA, C, SHAMANNA, D, and RAGHUNATHA Studies in blood sugar I, *Proc Ind Acad Sci*, 1938, vii, B 225
- 19 THORN, G W, NELSON, K R, and THORN, D W Study of the mechanism of edema associated with menstruation, *Endocrinology*, 1938, xxii, 155-163
- 20 THORN, G W, and EMERSON, K Rôle of gonadal and adrenal cortical hormones in production of edema, *ANN INT MED*, 1940, xiv, 757-769

CASE REPORTS

ANURIA FOLLOWING HEMOLYTIC REACTION TO BLOOD TRANSFUSION; RECOVERY FOLLOWING SPLANCHNIC BLOCK *

By H. RAYMOND PETERS, M.D., F.A.C.P., *Baltimore, Maryland*

MORTALITY from blood transfusions has been variously quoted in the past as from 0.2 to 1 per cent. While today it is to be hoped that the rate generally has fallen even below 0.2 per cent, transfusion of blood unfortunately will probably always carry with it a certain fatality rate.

Where the transfused blood is *compatible* fatalities are only rarely reported and usually are due to the development of pulmonary edema. This is commonly ascribed to overburdening of the right side of a previously weakened heart. Still more rarely cerebral hemorrhage or embolism and pulmonary embolism may occur.

The commonest cause of fatality from blood transfusion is the introduction of *incompatible* blood. Here, rarely, death may be almost instantaneous due to multiple thromboses, including the capillaries. More rarely death may occur directly due to exsanguination because of the hemorrhagic tendency following a hemolytic reaction.¹ But by far the most usual fatal mechanism after the injection of incompatible blood is the comparatively slow and undramatic onset of renal insufficiency. Once established, such insufficiency, with its concomitant anuria and uremia, is always of the gravest import.

It will probably never be possible to gauge accurately the true incidence of such transfusion reactions or estimate their fatality rate, for, as opposed to the comparatively few reported cases, certainly a very large number of such fatalities have never reached the literature. Such cases are not published for many obvious and understandable reasons—mainly that of grossly culpable errors in blood matching. Then too, at times, there is utter failure of the clinician to recognize the true nature and etiology of certain “kidney deaths” which followed transfusions. Occasional reports show it has been the pathologist alone who suggested the correct diagnosis.² In the comparatively scant literature on such transfusion anurias the mortality rate reaches high figures. Thus, DeGowin² in a frank discussion of his cases quotes one recovery in seven. Bordley³ in 17 cases compiled from the literature, cites 11 deaths.

Such high fatality rates in a condition unfortunate and tragic often by its very occurrence make us acutely aware of the ineffectiveness of the usually prescribed therapeutic measures. It would seem warranted, then, to stress any therapeutic approach which by trial appears to have been specifically helpful.

The following case is cited in which a very serious hemolytic reaction followed the transfusion of blood—not of a different, but of the homologous group.

* Received for publication May 14, 1940.

From the Department of Medicine, School of Medicine, University of Maryland.

The serological aspects of this case, in which a new agglutinin is designated, are completely covered elsewhere ⁴

CASE REPORT

M. E. P., a 32-year-old male, was admitted to the Mercy Hospital on November 22, 1939 with a history of recurrent attacks of headache, chills, fever and backache, associated with a leukopenia. The attacks began in January 1937, when he was operated on in another clinic for a perforated gastric ulcer. Postoperative course was complicated by a pneumonia associated with a leukopenia of 3000. A transfusion was given and the white count rose, the patient improved and was discharged. However, about six months later the attacks of headache, upper respiratory infection, chills and fever recurred. Clinical study is reported to have revealed nothing but infected tonsils and adenoids, with a hazy right antrum. Absolutely no drug history could be elicited from the patient, his wife or physician which would link up with the leukopenia. The tonsils and adenoids were removed and the right antrum drained on November 9, 1939 but the attacks recurred unabated. Because there had been apparent improvement in the initial attack in January 1937 from blood transfusion, the patient, who belongs to Group A (and as has later been ascertained, Rh minus) was given a transfusion on November 25, 1939 of 200 cc of fresh citrated blood. The blood of this first donor was also Group A but it has been shown since that he is Rh plus. About an hour after the transfusion the patient had a chill slightly more severe than those he had been having on the previous few days. No hemoglobinuria was noticed. The temperature dropped to a subnormal level and remained so for a week. Two other transfusions were then given from a second donor on November 27 and 30 respectively. This second donor's blood was Group A, subsequently shown to be Rh minus. No untoward symptoms followed transfusion from this donor. The patient remained temperature- and symptom-free and left the hospital on December 7, 1939. Two days later, however, he was readmitted on the service of Dr. M. C. Pincoffs with the same complaints of fever, chills, etc. On December 12 he was given a transfusion of 200 cc of fresh, citrated blood from the first donor (Group A, Rh plus) who had given blood to him 28 days previously on November 25. Twenty minutes after the transfusion was completed there was a violent shaking chill and the fever rose to 104.2 degrees. Adrenalin 1 cc was given, divided into three doses 10 minutes apart. One hour after the transfusion the patient developed bleeding from the nose and gums. This bleeding with nausea and vomiting, the latter at times bloody, persisted for days. A few ounces of urine were passed which showed hemoglobin but no red cells and soon complete suppression followed. Blood samples showed hemoglobinemia. The bleeding time was over 100 minutes and venepunctures oozed for many hours. Coagulation time was 60 minutes plus. Platelet count 144,000 (normal 500,000). The temperature dropped to and stayed subnormal. Blood pressure was 102 mm of mercury systolic and 60 diastolic (figure 1). Aside from the bleeding the patient felt "not much different than from his other chills." Therapy during the rest of the day was limited to the slow injection intravenously of one ampoule of Hartman's solution and small amounts of 5 per cent glucose. Fluids were given by mouth despite the vomiting.

Progress notes listed below present briefly the developing clinical picture and the therapy used.

Progress notes 12/13/39 After passing 60 cc urine at 6 a.m. has been completely anuric. Persistent lumbar pain, nausea and bloody vomiting continue. Blood urea 77 mg per 100 cc. The patient is jaundiced and has prompt direct positive Van den Bergh of 3.9 mg. (This, several days later, turned to the indirect type and finally became negative.) As the precise serologic etiology of this homologous group

reaction was undetermined at this time, the therapeutic administration of "correct group blood" was impossible. Therapy: Forced fluids by mouth and intravenously—the latter mostly glucose. In addition small amounts of intravenous Hartman's solution.

12/15/39 Still anuric. No definite change or improvement in general condition. Drowsy but mentally clear. Blood urea 110 mg per 100 c.c. (For blood and urine studies see table 1.)

12/16/39 No change in status of patient, save that edema is developing in the face, over the sacrum and tibiae and ascites is present. Therapy: In addition to the daily intravenous glucose 300 c.c. of Sorbitol (a pentose sugar) were given very slowly intravenously. Diathermy to each kidney for 15 minutes.

12/19/39 Still anuric with increasing edema and ascites. Blood urea 100 mg per 100 c.c. and creatinine 7.5 mg per 100 c.c. Therapy: Continuance of intravenous glucose daily with intravenous Sorbitol on several occasions.

12/20/39 Patient voided 75 c.c. of clear orange brown urine coincident with an enema. (Urine Sp. gr. 1.14, alkaline, albumin 4+ and benzidine test four +, no casts, occasional red cells.) Blood urea 128 mg and creatinine 9.6 mg. Carbon dioxide combining power of the blood plasma has always remained normal.

12/21/39 The anuria persists with edema increased. Patient feels and looks worse. Blood urea 132 mg.

12/22/39 Anasarca has increased with signs of fluid at both pleural bases. A pericardial friction rub is heard. Diathermy this morning (now for the third time) with no appreciable effect.

Splanchnic block done at 2:45 p.m. by Dr. D. Pessagno, according to the technique of Labat.⁵ Using 1 per cent novocaine, 40 c.c. were injected on each side, 25 c.c. in the region of the greater splanchnic and 15 c.c. in the region of the lesser splanchnic nerve. The procedure was done entirely retroperitoneally. The needle was inserted through the back lateral to the first lumbar vertebra on each side. Careful record of blood pressure showed only a comparatively slight drop immediately after the block and it returned to the preoperative level within 40 minutes.

Bladder dullness soon became evident and percussed increasingly higher until at 7:30 p.m. the patient voided 500 c.c. of dark orange urine following an enema. (Urine acid, sp. gr. 1.010, albumin 3+, no casts, eight red cells per high power field.)

12/24/39 Average daily urine output around 1275 c.c. Edema greatly relieved. However, blood urea is 216 mg per cent with creatinine of 9.4 mg. Because of the low blood and urine chlorides the intravenous glucose is given in saline and hypodermoclyses of normal salt initiated. There is less vomiting but patient is drowsy.

12/28/39 Patient is more alert and there is no nausea or vomiting. The blood urea and creatinine are falling. There has been so much diuresis (6000 c.c.) that despite the increasing edema fluids are still being forced to prevent hemoconcentration.

1/3/40 For the past several days patient has been able to take nourishing foods. Also oral fluid intake has risen and the blood urea has fallen to 48 mg with creatinine of 1.9 mg. Rather marked waterlogging had occurred by 12/29/39 and due to a satisfactory chemical balance hypodermoclyses were stopped. The edema is now definitely decreasing.

From this point on there was progressive improvement of the patient to normal. The urine, which had constantly shown traces of albumin with many red cells since diuresis began, became normal. Phenolsulphonphthalein tests gave results as follows: (December 30, 1939) 12 per cent, (January 7, 1940) 37 per cent, (January 17) 53 per cent, (April 18) 75 per cent. The specific gravity of the urine for over a month after the reaction remained constantly fixed between 1.009 and 1.011. However, in

three months' time the patient was able to concentrate to 1032. A moderate anemia (Hb 70 per cent, 10.5 grams) present after the reaction, with ferrous sulphate therapy was replaced by a normal blood picture

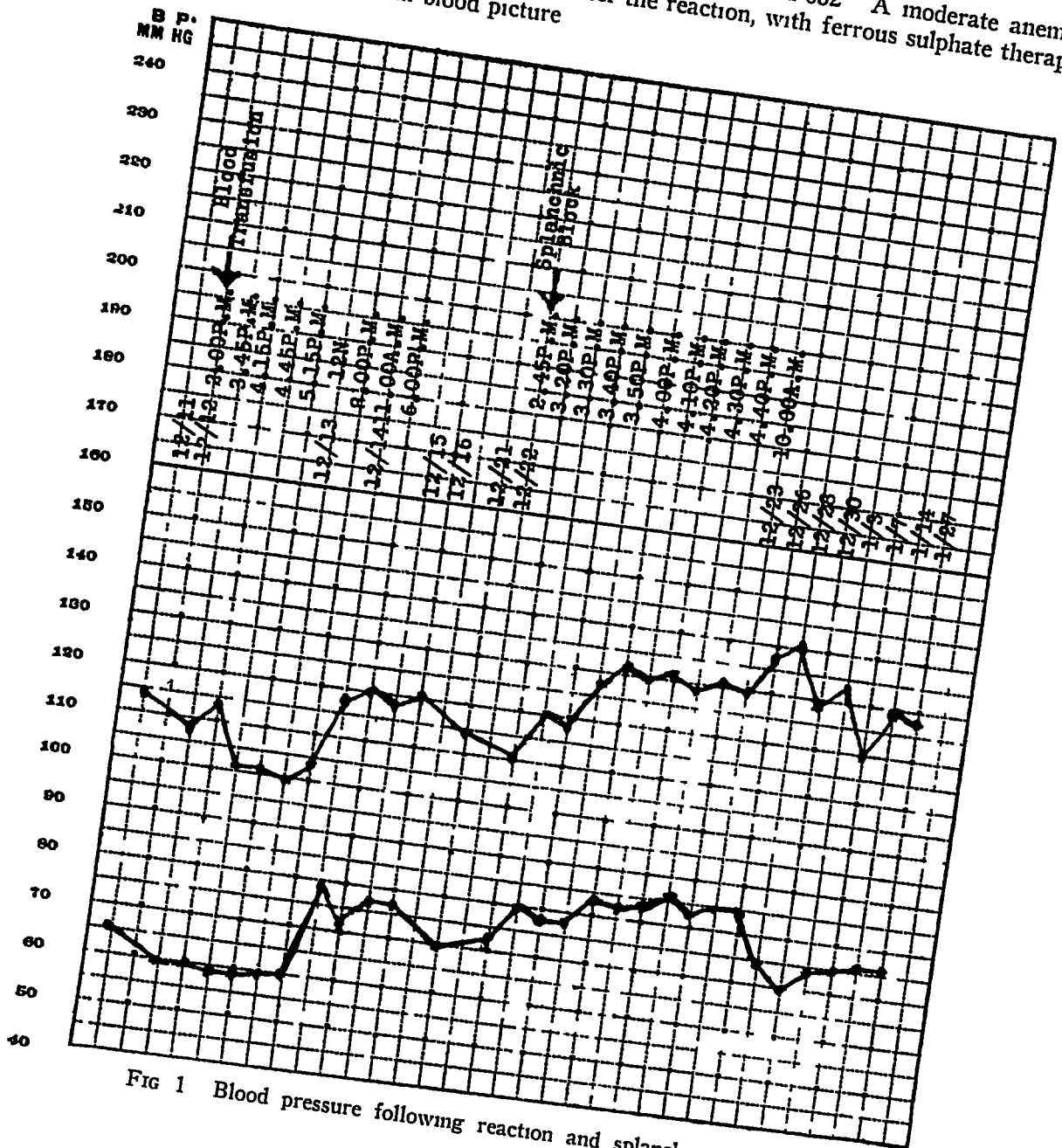


FIG 1 Blood pressure following reaction and splanchnic block

DISCUSSION

The mechanism involved in the suppression of renal function after hemolytic transfusion reactions is still not completely settled. There can be no doubt that the experiments of Baker and Dodds,⁶ Yorke and Nauss,⁷ Melnick et al.⁸ and DeGowin et al.⁹ show conclusively that precipitated hemoglobin does block the tubules in these cases, and, in the opinion of many, the whole picture of urinary suppression is thus solely and adequately explained. But, strangely, in a certain

proportion of fatal transfusion anurias such reported tubular obstruction, while present, has been notably sparse and quantitatively of a minor degree. Thus DeGowin² commenting on the obstructive theory feels that "the principal objection to it is that in many human cases not enough pathological evidence of tubular obstruction can be found." Warner¹⁰ likewise believes the pathology seen is "often not sufficient to explain the fatal uremia." Granting the part played by hemoglobin obstruction, evidence of further search for the complete mechanism involved is had in the variously proposed theories of chloride loss,¹¹ an allergic mechanism,¹² hemolytic nephrotoxic substances, etc. That these latter occur has also been seriously questioned.

There remains the by no means recent theory of *spasm of the renal vessels*. Mason and Mann¹³ in 1931 injected intravenously into animals the stroma of laked red cells and produced no apparent effect on the vessels. But the injection of extracted hemoglobin from such cells produced a "specific vasoconstrictor action on the vessels of the kidneys." Hesse and Filatov¹⁴ in 1933 obtained similar experimental results and later in the same year reported a hemolytic reaction in the human¹⁵ due to grossly mismatched blood. They attributed the intense backache in this and similar cases directly to the local renal vascular spasm. They were able almost immediately to transfuse properly matched blood (for which therapeutic procedure they claim priority) and, according to them, this brought about instant relief of the pain and the patient suffered no ill effects from the transfusion.

It would seem from available pathological reports that the kidneys of patients dying of transfusion anurias often present points of similarity to the kidneys observed in the so-called "reflex anurias," in which latter vasoconstriction plays such an important part. Today reflex anuria, while rare, is acknowledged as a clinical entity by a great number of observers. A typical example is the complete bilateral suppression of urine in a patient with calculus obstructing one ureter. Innumerable such cases are reported and among other ascribed causes of reflex anuria are hysteria, blows over the kidney, exposure to cold, fractured vertebrae, perinephritic abscess, plastic peritonitis, etc. Rubritius¹⁶ seems to have described the pathology of such kidneys quite thoroughly and accurately. He found that as opposed to former belief that the kidneys were pale and shrunken, reflex kidneys instead were "large, swollen and with full vessels." The vasoconstrictor action then would appear to be on the side of the efferent renal vessels, causing blood to stay pent up in the kidneys. Many continental writers have reiterated this belief and recently Cubitt,¹⁷ describing the kidneys as "enlarged and deeply congested," concurs in the angiospastic pathogenesis.

It would seem worthy of note, then, that not only has renal vasoconstriction been experimentally produced by intravenous hemoglobin injection but in the comparatively few reported autopsies after transfusion anuria the kidneys are grossly congested and swollen. Thus, Wiener¹⁸ declares the kidneys are usually found to be swollen with the pyramids appearing dark in color. Their vascular status, then, might well be analogous to that of the reflex kidney.

Experimentally irritation of the splanchnic nerves has been shown to cause oliguria and conversely section or anesthetic block will cause prolonged polyuria. In addition no untoward effects could be ascertained after splanchnic section^{19, 20}

As early as 1922 a therapeutic effort was made specifically to combat the renal vasoconstriction in reflex anuria. Neuwirt²¹ is generally credited with

having first successfully relieved such anuria by means of splanchnic block Rubritius²² reported success with this measure in seven out of eight cases Haslinger²³ and also Havlicek²⁴ each quote reflex anuric cases in which splanchnic block initiated diuresis

As an alternate procedure a few writers have advocated spinal anesthesia Thus, Hayes and Paramore²⁵ report the production of diuresis by this method in a case of plastic peritonitis with reflex anuria Cubitt²⁷ likewise tried spinal anesthesia in one case with success Compared to splanchnic block this procedure has received little attention as is evidenced by Cubitt's statement that this treatment (spinal anesthesia) had not to his knowledge been previously described

Splanchnic block in reflex anuria may have definite advantages over spinal anesthesia The application of a large quantity of anesthetic solution directly to the splanchnic plexus may, by its undiluted state and its mechanical bulk and pressure, more thoroughly interrupt the sympathetic flow According to Haslinger²³ the duration of splanchnic block would seem much longer than one would expect in spinal anesthesia Rubritius¹⁶ claims the possibility of peripheral "sub-station plexuses" creating reflex arcs of their own which necessitate a more peripheral, splanchnic block for their complete interruption Then too, as in some cases fibers making up the splanchnic nerves arise from as high as the fourth dorsal segment,²⁰ a spinal anesthetic to be at all efficient, must be given rather high Splanchnic block has never in our experience caused any appreciable fall in blood pressure As fall in blood pressure is ascribed as a cause for some anurias,²⁶ certainly spinal anesthesia, with its greater incidence of blood pressure fall, may possibly at times partially defeat its own purpose in an existing anuria Lassen and Husfeldt²⁷ in studying the effects of fall of blood pressure on the kidneys of normal individuals used spinal anesthesia to produce such fall and concluded that peripheral blood pressure need fall but a little below 70 mm of Hg before production of urine could cease entirely It would seem then that splanchnic block is the preferable procedure and in the hands of an experienced operator it is entirely innocuous

Cognizant, then, of the vasoconstrictive similarity of the reflex kidney to the "transfusion kidney" splanchnic block is suggested as an added therapeutic measure against the latter To my knowledge this particular procedure has not before been used in such anurias The use of spinal anesthesia in a case of transfusion anuria has been reported by Johnson and Conway²⁸ They saw no specific effect and, despite later diuresis, uremic death occurred DeGowin² in reporting seven transfusion anurias used spinal anesthesia in one case—incidentally the only case which recovered He notes, however, that the clinicians regarded the recovery as spontaneous

It cannot be too urgently stressed that whatever, if any, value splanchnic block may possess in transfusion anurias, it should only be considered the key for unlocking the door to subsequent judicious treatment The establishment of diuresis, while an essential step, far from insures recovery for the patient Reference to figure 2 makes evident the very stormy period following diuresis in the case herein reported Careful observation of the chemical balance of the patient may often clearly guide the treatment The excellent advice of Cabot and Iber²⁹ and Jeghers and Bakst²⁶ regarding anurias can well be heeded here The kidneys must have a continuously positive water balance Hence, dehydra-

tion must be watched for, prevented or treated. As much as 5000 to 7000 c c of fluid daily can be lost in some cases by vomiting, diarrhea, gastric retention and by way of the lungs and skin—yet with no urine passed. Fluids then must be forced (often almost entirely intravenously) even up to 6000 c c or over daily. If intravenous injection is slow 'overburdening of the circulation' will not occur and even this danger is less than that of dehydration. As to the nature of the intravenous fluids judgment must be used. Saline is best to overcome dehydration for the sodium ion is necessary to fix the water to the tissues. In higher strengths, if necessary, it must be used to raise lowered blood chlorides. However, because saline is taken up by the tissues, it may not be as good in certain stages of an oliguria as glucose solutions, for the water of a glucose solution is more available for renal excretion. This is more true of hypertonic glucose. Both saline and glucose should be used, watching the chemical balance. Blood chloride and blood sodium levels do not always parallel each other. As pointed out by Jeghers and Bakst²⁶ few laboratories are equipped to perform routine sodium determinations. However, they add "indirectly, the sodium level can be roughly surmised in many cases from a comparison of the blood chloride level and the carbon dioxide combining power. If the carbon dioxide combining power is high (alkalosis) and the blood chloride level is low, then the sodium level is probably near normal. Conversely a low carbon dioxide combining power (acidosis) with normal or slightly low blood chloride level speaks for the presence of an hyponatremia." Since the kidneys, in the presence of an alkaline urine, readily excrete hemoglobin as oxyhemoglobin Baker and Dodds⁶ advocate the giving of alkalis in treatment and this seems theoretically plausible. The carbon dioxide combining power should be watched, however, to guard against alkalosis.³⁰ Diathermy to the kidneys has had a few reported successes and many failures. Its value at any stage must still be proved. Transfusions of truly compatible blood have been advocated after a reaction due to mis-matched blood.¹⁸ Under such circumstances the procedure should be considered provided one is sure of having truly matched blood at this stage. Decapsulation of the kidneys in any anuria is today in rather wide disfavor.²⁹

Finally, it must be remembered that, no matter how successfully splanchnic block may relieve renal vasoconstriction, in any given case one may still have kidneys in which widespread tubular epithelial degeneration has developed and the prognosis must be judged accordingly. Early initiation of all the outlined therapeutic measures would seem of paramount importance.

SUMMARY

1 A case is presented in which a hemolytic reaction and prolonged anuria developed following transfusion of blood of the homologous group. After failure of other measures for nine days, diuresis followed within a few hours after a splanchnic block and there was ultimate complete recovery of the patient.

2 Accrued evidence is offered in favor of a vasoconstrictive renal element in transfusion anuria similar to that of the so-called "reflex anuria." Splanchnic block would seem a preferable and innocuous measure against such renal angiospasm.

3 It is stressed that splanchnic block, even if successful in its purpose, is only "the key which unlocks the door" to further judicious therapy.

BIBLIOGRAPHY

- 1 PARR, L W, and KRISCHNER, H Hemolytic transfusion fatality with donor and recipient in the same blood group, *Jr Am Med Assoc*, 1932, *xcviii*, 47
- ABRAMSON, M Hemolytic transfusion reaction with death, *Jr Lancet*, 1935, *lv*, 805
- 2 DEGOWIN, E L Grave sequelae of blood transfusion, *ANN INT MED*, 1938, *xi*, 1777
- 3 BORDLEY, J Reactions following transfusion of blood with urinary suppression, *Arch Int Med*, 1931, *xlvi*, 288
- 4 WIENER, A S, and PETERS, H R Hemolytic reactions following transfusion of blood of the homologous group, *ANN INT MED*, 1940, *xiii*, 2306
- 5 LABAT, G Regional anesthesia, 1924, W B Saunders and Co, Philadelphia, Pa
- 6 BAKER, S L, and DODDS, E C Obstruction of the renal tubules during the excretion of hemoglobin, *Brit Jr Exper Path*, 1925, *vi*, 247
- 7 YORKE, W, and NAUSS, R W The mechanism of the production of suppression of urine in Blackwater Fever, *Ann Trop Med and Parasit*, 1911, *v*, 287
- 8 MELNICK, D, BURACK, E, and COWGILL, G R Development of incompatibility in dogs by repeated infusion of red blood cells, *Proc Soc Exper Biol and Med*, 1938, *xxxiii*, 616
- 9 DEGOWIN, E L, OSTERHAGEN, H F, and ANDIERCH, M Renal insufficiency from blood transfusion I Relation to urinary acidity, *Arch Int Med*, 1937, *lix*, 432
- 10 WARNER, E Comments following paper by DEGOWIN, E L Blood transfusion reactions, *Jr Iowa Med Soc*, 1939, *xxix*, 20
- 11 BROWN, G E, EUSTERMANN, G B, HARTMAN, H R, and ROWNTREE, L G Toxic nephritis in pyloric and duodenal obstruction Renal insufficiency complicating gastric tetany, *Arch Int Med*, 1923, *xxxii*, 425
- ROOT, H F, and HENSON, P P Postoperative suppression of urine relieved by intravenous injection of hypertonic salt, *Jr Am Med Assoc*, 1931, *xcvi*, 540
- 12 LONGCOPE, W T, and RACKEMANN, F M Severe renal insufficiency associated with attacks of urticaria in hypersensitive individuals, *Jr Urol*, 1917, *ii*, 351
- 13 MASON, J B, and MANN, F C Effect of hemoglobin on the volume of the kidneys, *Am Jr. Physiol*, 1931, *xcviii*, 181
- 14 HESSE, E, and FILATOV, A Experimentelle Untersuchungen über das Wesen des hamolytischen Shocks bei der Bluttransfusion und die therapeutische Beeinflussung desselben I Die Nierenfunktionsstörungen im akuten Experiment, *Ztschr f d ges exper Med*, 1933, *lxxxvi*, 211
- 15 HESSE, E, and FILATOV, A Die klinische Bestätigung der möglichkeit der Behandlung des hamolytischen Shocks bei der Bluttransfusion nach unserer Methode, *Zentralbl f Chir*, 1933, *lx*, 851
- 16 RUBRITUS, H Infection and function of urogenital system, *Wien klin Wchnschr*, 1925, *xxxviii*, 37
- Reflex anuria, *Wien klin Wchnschr*, 1925, *xxxviii*, 749
- 17 CUBITT, A W The problem of anuria A review of recent work on renal physiology, with report of two cases, *Brit Jr Surg*, 1936, *xxiv*, 215
- 18 WIENER, A S Blood groups and blood transfusion, 2nd Edition, 1939, Charles C Thomas, Baltimore
- 19 MILLIKEN, L F, and KARR, W G The influence of the nerves on kidney function in relation to the problem of renal sympathectomy, *Jr Urol*, 1925, *xiii*, 1
- 20 CALDWELL, J M, JR, MARX, M, and ROWNTREE, L G Renal function after bilateral denervation of the kidney in normal dogs, *Jr Urol*, 1931, *xxv*, 351
- 21 NEUWIRT, K Ein Beitrag zur Therapie der reflex Anuria, *Ztschr f urol Chir*, 1922, *ii*, 75
- 22 RUBRITUS, H Die chirurgische Behandlung der Niereninsuffizienz, *Wien klin Wchnschr*, 1930, *xliii*, 676
- EISENDRATH, D N Transaction of the Chicago Urological Society, Anuria, *Jr Urol*, 1931, *xxv*, 421

- 23 HASLINGER, K Zur Therapie der reflectorischen Anurie, *Ztsch f Urol*, 1927, *xxi*, 174
- 24 HAVLICEK, H Blocking splanchnic nerve to arrest vascular spasm in the kidney, *Zentralbl f inn Md*, 1925, *xlvi*, 465-470
- 25 HAYES, D S, and PARAMORE, R H Anuria treated with spinal anaesthesia, *Lancet*, 1935, *ii*, 554
- 26 JEGHERS, H, and BAKST, H J The syndrome of extrarenal azotemia, *ANN INT MED*, 1938, *xi*, 1861
- 27 LASSEN, H C A, and HUSFELDT, E Kidney function and blood pressure, *Jr Clin Invest*, 1934, *xiii*, 263
- 28 JOHNSON, R H, and CONWAY, J F Urinary suppression and uremia following transfusion of blood, *Am Jr Obst and Gynec*, 1933, *xxvi*, 255
- 29 CABOT, H, and IBER, F C Anuria, *Proc Staff Meet Mayo Clin*, 1933, *viii*, 354
- 30 MANDRIEBAUM, H Hemolytic reaction following blood transfusion Report of a case of intra-group incompatibility, *ANN INT MED*, 1939, *xii*, 1699

EQUINE ENCEPHALOMYELITIS IN A LABORATORY TECHNICIAN WITH RECOVERY *

By HERMAN GOLD, M D, and BETTYLEE HAMPIL, Sc D,
Glenolden, Pennsylvania

SINCE Meyer's original report of equine encephalomyelitis in man,¹ many cases of this disease have been described in the medical literature. Excellent reviews have been published by Fothergill² and by Olitsky.³ Recently a proved case of encephalomyelitis in a laboratory technician was reported by Fothergill, Holden, and Wyckoff.⁴ It resulted in death and the virus (Western type) was recovered from the brain at autopsy. We wish to report another laboratory infection. Our case is interesting because we were able, fortunately, to determine the virulence of the infective agent, its portal of entry, and the incubation period. Moreover, the titer of antiviral protective antibodies present in the blood of our patient before infection occurred is also known. In addition, the clinical record was dramatized by the development of acute Parkinsonism. Finally, large doses of a specific antiserum of high potency were used intravenously, intramuscularly and intraspinally. Complete recovery ensued.

At the outset we wish to state that we have not formed any set opinion as to the value of the specific serotherapy employed in this case. We are well aware of the generally accepted belief, so aptly stated by J. E. Gordon,⁵ that "Medicine has little to offer in respect to a specific attack on acute virus disease. Immunologic principle is opposed to success because once a virus has established itself inside the cells—and usually this occurs by the time symptoms are definite—little benefit can be expected from antibodies transported by blood or lymph and acting extracellularly, even though given in large amounts." However, in the absence of other means of treatment our experience warrants the use of a highly potent serum in large quantities if available. It may serve to limit the spread of the disease and thus aid in recovery.

* Received for publication August 24, 1940

From the Medical Research Division, Sharp and Dohme

CASE REPORT

J R a white male, 29 years of age, came in contact with encephalomyelitis virus for the first time on February 8, 1939, when he was assigned to assist in experimental work in the encephalomyelitis vaccine division of the Mulford Biological Laboratories, Sharp and Dohme. His work consisted of inoculating eggs with the virus (Western type), removing the diseased embryos and grinding them in a mortar. On March 2, 1939, he was transferred to duties connected with the preparation of the vaccine on a production scale, and thereafter assisted in harvesting and grinding the embryos in large quantities. Sterile gowns, caps, gloves, and masks were worn throughout the operation. Minor injuries and accidents were regarded by the personnel as serious and were reported promptly.

On April 3, 1939 samples of blood were drawn from J R and other members of the staff to determine the presence of neutralizing antibodies in their sera. Tests were done in duplicate by Dr J W Beard, of Duke University and by one of us (B H). The results were negative. Fifteen days later, April 18, 1939, at 3 50 p m, while cracking a diseased egg* over the edge of a funnel, some of its liquid contents splashed into the patient's face, close to the right eye. He reported slight burning of the right eye. The patient immediately washed his face with 90 per cent alcohol and reported to the first aid dispensary. Examination by Dr LeRoy Wenger failed to reveal any irritation of the eyes. Treatment consisted of thorough washing of the face with soap and water and instillation of a few drops of 10 per cent Cargentos (Protein Silver Mild) into the right eye which was flushed out before and after with boric acid solution.

The patient returned to work but reported to the dispensary on April 19, 20 and 21, when Dr Wenger found no evidence of disease. On April 24, the patient did not report to work because of illness. Dr Wenger called at his home and elicited this additional history. He had worked up to Saturday noon (April 22). During that morning the patient had noted pain in back of the forehead and between the temples. This became worse so that when he got home he went straight to bed and slept until Sunday noon (April 23). Severe headache was present on awakening. The family physician, Dr H B Conaway, was then called in. A diagnosis of grippe was made and suitable medication ordered. Examination by Dr Wenger revealed a coated tongue and some injection of the throat. No neurological abnormality was found. The temperature was 100.3° F, and the pulse 85.

The patient was reexamined the next morning at 11 a m. Severe headache was still present. At this time Dr Wenger noted that the patient was slightly stuporous and had to be roused to get ordinary answers. Temperature was 102.2° F, and pulse rate was 100. The neck showed some stiffness. The arm and patellar reflexes were diminished. No other abnormal signs were found. At 2 p m the patient had 103.2° F fever and a pulse of 120. After consultation with Dr Conaway, who had

* The history of the virus with which this patient became infected is as follows. The Western type virus (Iowa 1937 strain) was received at the Mulford Laboratories from the Bureau of Animal Industry, Washington, D C, in the seventh guinea pig brain passage. It was transferred once to guinea pigs and thence to chick embryos. Twenty-ninth chick passage material was being harvested at the time of the accident. On April 7, 1939, or 11 days before the accident, the twenty-seventh passage of this strain of virus had been tested on guinea pigs for infectivity by the subcutaneous route of inoculation. Young guinea pigs weighing 250 grams were used. Two pigs were injected with 0.1 c c each, two with 0.25 c c, and two with 0.5 c c. The material used for the guinea pig injections was simultaneously titrated on 21 day old Swiss mice by the intracerebral injection of 0.03 c c of serial dilutions in tenths. The 10⁻⁵ dilution killed mice, thus, 1 c c contained approximately 3,300,000 mouse intracerebral doses. All six guinea pigs developed marked symptoms of encephalomyelitis. One of each group died. The remaining three animals showed severe emaciation for six weeks, at which time they were destroyed. This observation indicates that the virus was highly infectious when injected peripherally.

independently verified the serious turn in the patient's condition, it was decided to hospitalize him for spinal fluid study. Upon his admission to the Roxborough Memorial Hospital of Philadelphia, on April 25, 1939, at 7 25 p m, the attending resident, Dr T Greenspon, found marked rigidity of the neck, a bilious kidney, Kernig sign (more marked on the left), and absent abdominal reflexes. Triceps, and patellar reflexes were normal. Babinski sign was negative. Lancet, 1935, the patient was at times disoriented and quite stuporous, he answered questions with a fair degree of accuracy. The spinal fluid was faintly cloudy, under 14 mm of mercury pressure, and contained 600 white cells. There were no organisms on direct smear. White blood cell count was 14,600, polymorphonuclears 84 per cent, lymphocytes 4 per cent, monocytes 8 per cent. Rectal temperature was 104° F, 140, respirations 28. When one of us (H G) saw the patient for the first time at 9 30 p m, he was found smoking in bed, very nervous and jumpy, and sweating profusely. A coarse tremor of the hands was noted. Skin and eye tests for horse serum sensitivity were negative. Dr Sherman F Gilpin of Philadelphia, a neurological consultant, saw the patient at 10 30 p m and confirmed the above findings except for a decrease in the reflexes of the arms. Sensation to pin-prick was apparently intact. The cranial nerves appeared normal. Throughout the examination the patient muttered in a delirium but was otherwise fairly cooperative. Dr Gilpin agreed with our presumptive diagnosis of equine encephalomyelitis, and the specific therapy we proposed to use. In addition, he suggested the trial of sulfanilamide.

Five hundred fifty c c of anti-encephalomyelitis immune horse serum* were then given intravenously by gravity method without any untoward reaction except for a few hives. Spinal puncture was repeated. A turbid fluid under 14 mm of mercury pressure dropped out slowly. After removing about 40 c c of spinal fluid, 50 c c of the immune serum were injected intrathecally without any reaction. Careful bacteriological study of a sample of this spinal fluid done at the Mulford Laboratories was completely negative. It was obvious that a marked change for the worse had taken place in the course of one hour previous to the serum injection. The patient had become deeply stuporous and completely disoriented. At 1 20 a m a severe chill occurred which lasted 25 minutes. Sulfanilamide, gr xxx, was given by mouth followed by gr xv every four hours. This was discontinued at the end of 36 hours because of the lack of any beneficial effect. Phenobarbital was also given for the control of restlessness.

On April 26, at 12 30 p m, the clinical picture was that of a deep coma with increased rigidity of the neck, definite ankle clonus, knee jerks which varied in their response, coarse tremors of the face and extremities and cyanosis of lips and nails. Temperature was 104.2° F, pulse 130, respirations 40. Blood pressure was 150 mm of mercury systolic and 80 mm diastolic. A spinal tap was repeated. The fluid was distinctly turbid and dropped out slowly. Its cell count was 1899. Globulin was increased. Sugar (Folin) was 95 mg per cent, chlorides were 692 mg per cent. Sixty-five c c of spinal fluid were removed, and 50 c c of immune serum were injected in the spinal canal. Following the tap, 450 c c of the serum were given intravenously by gravity. During the injection the patient perspired profusely and exhibited signs of fleeting paresis of the left side of the face. Throughout the day there occurred paroxysms of fine clonic contractions of the right hand and forearm with tremors of the left hand on motion. There was urinary incontinence. A specimen of urine revealed the presence of a faint trace of albumin and an occasional white blood cell. The blood count showed hemoglobin 75 per cent, red blood cell count 4,360,000, white blood cell count 15,450, polymorphonuclears 96 per cent, lymphocytes 4 per cent.

On April 27, at 9 a m, the patient was definitely more rigid and stuporous and could not be aroused. The left hand showed ulnar deviation with the thumb and

* Supplied by Lederle Laboratories, Inc, through the courtesy of Mr S D Beard

forefinger pressed together. The Kernig sign was more marked on the right. No ankle clonus. A spinal tap was done. Spinal pressure was 10 mm of mercury. Negative Queckenstedt sign. The fluid was less cloudy, but after standing a large number of flecks were seen on stirring. About 15 c c of fluid were removed and the pressure dropped to 2 mm of mercury. Its cell count was 850. Polymorphonuclears 75 per cent, lymphocytes 25 per cent. Smear and culture were negative. After the tap was done, 350 c c of immune serum were given intravenously. There was no reaction but a chill which lasted 35 minutes. That night the patient was still in deep stupor but appeared to be less rigid. Coarse tremors of the left hand were present. At midnight the patient became conscious and talked rationally. The temperature was 101.3° F, pulse 130, respirations 32. Laboratory studies reported the blood sugar as 90 mg per cent, the blood chloride as 432 mg per cent of whole blood, and the blood urea as 15 mg per cent.

On the following morning the patient was definitely improved. The rigidity of the neck was lessened and the upper extremities which had been stiff showed a normal tone. The Kernig sign was negative on the left and only suggestively positive on the right. The deep reflexes were normal and the patient was able to protrude the tongue. Fifty c c of immune serum were given intramuscularly at 9 a m. Due to a sudden jerk, the needle broke at the hub. A hurried search was conducted, but the missing part remained buried in the left thigh. Another 50 c c of serum were injected at 9 45 p m. The patient was better, responded to painful stimuli, and actually recognized the visiting physicians. Because of the profuse sweating, sodium chloride grs v four times a day was prescribed. Temperature was 100.4° F, pulse 120, and respirations 34.

On April 29, at 11 30 a m, the patient's sensorium was clear. He was oriented as to place and events and recognized his family. Upon request he attempted to smile. The neck was still stiff and the spine appeared to be more sensitive to pain. A spinal tap revealed a clear fluid (a few flecks were seen on stirring) with a cell count of 276. Globulin was normal. About 35 c c of fluid were removed. Forty-five c c of anti-serum were then injected intramuscularly. Control of bowels and bladder had returned. At 9 p m the patient's facial expression was more relaxed. He occasionally smiled and expressed interest in the place of work. Breathing was quiet and regular in contrast to the previous night, when it was labored. The Kernig sign was negative. Temperature was 101.3° F, pulse 120, respirations 22. The red blood cell count was 4,290,000, hemoglobin was 75 per cent, white blood cell count 15,850, polymorphonuclears 92 per cent, lymphocytes 8 per cent.

On April 30, the patient showed steady improvement both mentally and neurologically. He asked for the newspapers and for a smoke. He understood and answered questions clearly. He complained of pain along both sternomastoid muscles, left shoulder and thigh, made worse by motion. The postcervical and inguinal nodes were palpable and slightly tender (serum sickness?). Perspiration was decreasing. The neck and spine showed decreased spasticity. The rest of the musculature showed normal tone. The biceps reflexes were exaggerated but equal. The triceps reflex was normal. The abdominal and cremasteric reflexes were absent. The knee jerk was slightly increased, and there was a slightly positive Kernig sign on the right side. No ankle clonus. Babinski sign was negative. The temperature was 99.3° F, pulse 120, respirations 28.

Next day the patient became very drowsy and was awakened with a great deal of difficulty. It was difficult to make him understand even simple questions. Urinary incontinence developed during the night. There was no change in the neurological picture. Adenopathy was the same. A punctate erythema and a few hives appeared on the chest. A spinal tap was done at 12 15 p m. Blood was encountered. However, the fourth specimen was clear. The fluid dropped out slowly, but there was

no block. Fifteen cc were removed. Fifty cc of 50 per cent sucrose were given intravenously and 2 cc of histaminase were injected intramuscularly in each thigh. The patient was seen again at 9 30 p m. He had slept throughout the afternoon, drenched in sweat. He could now be aroused more easily but could not remain awake for more than a few minutes. The rash had disappeared from the chest but was present on the knees. The arms were painful. Muscle tone was normal. The neck was definitely less stiff. A coarse tremor of the tongue and hands was noted. Temperature was 100° F, pulse 104, respirations 24.

On May 2, the patient was alert and rational at noon, but when seen at 5 00 p m he could hardly be aroused. The erythema had disappeared, but a few hives came out throughout the day. Muscle tenderness was still present. Neck stiffness was unchanged. Kernig sign was positive on the left. A fine slow tremor of the eyelids and muscles around the mouth was noted. Two cc of histaminase were injected intramuscularly in each thigh. Temperature was 101 1° F, pulse 104, respirations 34. The blood Wassermann test was negative, the blood chloride was 464 mg per cent of whole blood, and the blood urea was 13 mg per cent. The urine was alkaline, specific gravity 1 050, it showed a faint trace of albumin, an occasional dark granular cast, an occasional epithelial cell, and a few white blood cells.

The patient was much improved when seen on May 3. He was wide awake and able to raise both arms. He grasped objects more easily and with lessened tremor of the hands. The neck was not as stiff and the knee jerks were less exaggerated. Profuse sweating was still present. An occasional hive and soreness of muscles of the left arm were noted. Temperature was 100° F, pulse 96, respirations 24. A spinal tap was done at 11 15 a m. The pressure was 12 mm of mercury. On compression of the jugular veins, it went up to 26 mm but dropped promptly on release. The fluid was clear with no flecks or sediment. About 30 cc were drained. Final pressure was 2 mm. The cell count was 47, with 80-90 per cent lymphocytes. Globulin was negative. The red blood cell count was 4,160,000, hemoglobin 75 per cent, white blood cell count 15,850, polymorphonuclears 78 per cent, lymphocytes 22 per cent. Two cc of histaminase were injected in each thigh.

On May 4, the patient had a good day. He was able to keep awake and moved around in bed with ease. Facial expression was almost normal. Tremors of the lids, tongue, and left hand were still present. Abdominal reflexes were elicited for the first time. The only evidence of serum sickness was soreness in the left deltoid. Temperature was 99° F, pulse 84, respirations 24. Two cc of histaminase were injected in each thigh. Passive and active exercises were carried out to prevent atrophy which was quite noticeable.

We saw the patient again next day at 4 15 p m, when he appeared improved. The neck could be bent to 15° short of its normal range. There were no signs of serum sickness. Temperature 98° F, pulse 80, respirations 20. At 6 p m the nurse noticed that the patient had become very listless and was staring into space. He seemed depressed and emotionally upset. He complained of frontal headache, and the pupils were widely dilated. Two cc of histaminase were injected in the muscles of the thigh, and 50 cc of 50 per cent sucrose were given intravenously for possible cerebral edema. The patient had a poor night.

When seen by us the next morning at 11 o'clock, the patient's appearance and mental reactions were decidedly worse. He was listless and had a vacant stare. There was a marked tremor of the lids, tongue, and muscles around the mouth. The patient did not talk readily and spoke in a very low tone. He refused food and stated that he had an ache above the eyes and that he had not slept well. There was profuse sweating. Both eyes showed conjunctival injection and swelling (serum sickness?). Neurological signs showed improvement except for the marked tremor of the head. A spinal tap was done. The fluid was clear (few flecks on stirring) and

under 6 mm of mercury pressure about 10 cc were removed. Cell count was 31 with 90 per cent lymphocytes. Globulin was normal. Four cc of histaminase were given intramuscularly. Temperature 97.3° F, pulse 68, respirations 20.

On May 7, the nurse noted that the patient had difficulty in swallowing and breathing. He presented the picture of severe Parkinsonism with mutism. Temperature 98° F, pulse 96, respirations 20.

The next day, Dr. A. M. Ornstein, of Philadelphia, saw the patient in consultation. His report read as follows:

"The general appearance of the patient is striking and at once diagnostic of the nature of the motor disability, i.e., extra-pyramidal akinesia or the pseudo-catatonic state of Parkinsonism. He lies immobile on his back and his eyes are fixed in the position of staring ahead. He does not turn his head in the direction of the speaker, but his intention to do so is indicated by the slow lateral associated movements of the eyeballs after it is insisted that he look in one direction or the other. The arms are in a semiflexed position with the hands resting on the body, the fingers are closely opposed to one another with the tip of the thumb opposed to the palmar surfaces of the index and middle fingers, the characteristic position of Parkinsonism, being more in evidence in the right hand than the left. The lower limbs are in extension and the patient is capable of moving the extremities but in a very slow manner, both the upper and lower limbs being markedly hypertonic, and on passive motion the increased tone is recognized as rigidity of the extra-pyramidal type, the upper limbs show the characteristic cogwheel type of hypertonus at the elbows and wrists.

"There are hyperkinetic features in the clinical picture and they are confined to the eyelids and tongue. The eyelids show a constant coarse tremor, the frequency of about three to five a second but fairly irregular. Occasionally there occurs blepharospasm with complete closure of the eyes, at the cessation of which the tremor is again in evidence. The eyes are moved laterally and upward in a normal fashion and with good associated innervation, but convergence is deficient. Pupils are dilated but equal and react to light and accommodation. Ophthalmoscopic examination discloses no pathological changes in the discs, vessels, or retinæ. No nystagmus was noted. The wrinkling of the brow is slightly possible, closure of the lids is complete but not forceful, and retraction of the corners of the mouth is barely possible. The patient hardly opens the mouth and attempts to protrude the tongue but can bring only the tip of it beyond the dental line and it is coarsely tremulous. The mouth is full of stagnant thick saliva which fills the fauces, and the patient occasionally swallows with deliberate effort to down the excess fluid accumulated in his throat. Vital sensation is apparently preserved, but because of the patient's inability to speak gnostic sensibilities could not be tested. During this examination the patient was totally mute. The tendon reflexes at the elbows are elicited but not pathological, the patellar tendon reflexes are bilaterally hyperactive to the same degree, the Achilles jerks are equal and normal, the plantar reflexes are of the normal flexor type. The lower abdominal and cremasteric reflexes are absent, the upper abdominals were elicited quite normally. No tremor of the extremities was seen. There is marked resistance on passive flexion of the head and extension of the legs producing positive Kernig and rigid neck signs, but these are only apparent because the resistance is due to hypertonicity rather than reflex meningeal contraction.

"The present clinical picture is that of a severe and widespread mesencephalitis producing a very marked state of Parkinsonian akinesia associated with a hyperkinetic phenomenon affecting the eyelids and tongue as described above, the mutism is part of the state of akinesia. Because of the latter symptom it is difficult to examine the psychical reactions of the patient, but he impresses me as being mentally clear, since he showed fairly good apperception and attention and cooperation as far as it was possible. I envisage a pathological involvement of both lenticular nuclei,

especially the globus pallidus segment, the substantia nigra and possibly the red nuclei because of the constant slow tic-like tremor of the eyelids apart from the intermittent blepharospasm. The development of the basal ganglia symptom-complex in the third week of the disease, at a time when all indications of the infectious process had subsided indicates pathological injury of the aforementioned structures by perivascular cellular infiltration and ganglion cell degeneration.

"When acute Parkinsonism develops in the course of epidemic encephalitis the disability is permanent, and I see no reason to believe otherwise in this case of equine encephalomyelitis virus. However, it is possible for improvement to take place with disappearance of edema so that the patient may become ambulant. If this is going to take place, there should be indications of clinical improvement within the next three to six weeks. Amphetamine sulphate may be tried empirically at the present time in an effort to stimulate the psyche into some degree of spontaneity, 5 mg three times a day and gradually increased according to the effects."

May 9 Temperature 98.4° F, pulse 112, respirations 24. Patient shows marked weakness. A large amount of mucus was aspirated from the throat. Dr. Ornstein's therapeutic suggestions put into effect.

May 10 Some hives appeared on the extremities. Conjunctivae are injected. When addressed the patient is able to interrupt his vacant stare for a few minutes. Now able to expectorate. Two cc of histaminase were given intramuscularly in each thigh. Amphetamine sulphate, 5 mg, given three times a day.

May 11 There is no change in the clinical picture except that the tremor of the lids is not as marked. Patient sits up to carry out muscular exercises. Urticaria is so pronounced that four doses of epinephrine hydrochloride were required for relief. Four cc of histaminase were given intramuscularly. Fluid intake good. Temperature 99° F, pulse 120, respiration 20.

May 12 Body is still covered with hives. Epinephrine hydrochloride was given subcutaneously and in the eyes. Patient is able to sit up in bed without support. No change in the muscular rigidity or mutism. Fifty cc of 50 per cent sucrose were given intravenously. Four cc of histaminase were injected intramuscularly.

May 13 Patient is more alert today. He smiles occasionally, reads the newspaper and moves around in bed with greater ease, but can't open his mouth and can't chew. Perspires a great deal. Hives still present. Two cc of histaminase given. One ounce of vitamin B complex taken by mouth, 50 cc of 50 per cent sucrose given by vein.

May 15 Temperature has remained normal. Patient is much improved. Slow blinking, occasional blepharospasm and staring still present. Able to open the mouth a bit wider, but can't protrude the tongue. The chin and lips quiver and tremble on effort. Began to talk yesterday morning. Utters single words. Muscle and neck rigidity are decreased and movements of the hands are more regular. Negative Kernig sign. No hives. Hemoglobin 75 per cent, red blood cell count 4,222,000, white blood cell count 10,350, polymorphonuclears 62 per cent, lymphocytes 38 per cent.

May 17 Patient shows decided improvement. His speech is clear. He does not stare as much and laughs a great deal. Winking, though present, is pronounced only after excitement. Able to open the mouth fully and to protrude the tongue. Right eye shows deficient convergence. Muscle tone is returning to normal. Coordination improved. Patient tried to stand on scales, but felt too weak.

May 18 Out of bed for ½-1 hour. Tired easily. Only medication given is Amphetamine sulphate (gr ½ t.i.d.) and Vitamin B complex, one ounce daily.

May 19 Speech shows marked improvement. Powers of concentration excellent. Playing cards with the nurse. High caloric intake.

May 20 Patient brushed his own teeth and fed himself. Walks around the room with ease and gait is grossly normal. Muscle tone normal. Neurological ex-

amination negative, except for occasional tremors of lids, tongue, and lips. Amphetamine sulphate by mouth was discontinued.

May 21 Walking alone for considerable distance. Tremor of lids is more pronounced when tired.

May 23 Needle removed by Dr. T. J. Fleming under local anesthesia and fluoroscopic control. Excitement has made tremor more intense. Preoperative urine examination was negative.

May 26 Walking well. Tremor of lids still present. It is of slow type and especially noticeable on closing of lids. Tremor of tongue lessened.

May 30 Patient feels very well after a long walk. Appetite good. Gaining weight. Muscle power and tone normal. Good performance of fine motions. Memory of present events is good. Patient does not remember anything that transpired during the first 12 days after admission to the hospital. Four capsules of Vitamin B complex given daily.

June 2 Patient is very active. He still has slight tremors of the lids. Good muscle control except over the left foot, which he stamps down on walking.

June 3 Discharged from the hospital. Seen by Dr. Ornstein at his office for neurological check up. Results of examination were as follows:

"Neurological reexamination today discloses the very startling fact that the acute striatal status of complete akinesia and segmental tremor has disappeared! The patient appears to be as normal in the motor sense as one can expect except for a slight dysergia in the use of the left lower limb in walking which the patient is aware of in the form of a little heaviness of that limb when tired, and the left arm does not swing as much as the right, but it is not motionless. The muscle tone is normal in all four limbs and there is not the slightest suggestion of the cogwheel type of rigidity. The extended hands show no tremor of the finger tips, but the eyelids flutter abnormally when he shuts his eyes and the previously continuous twitching of the lids is not present today. There is no obvious tremor of the facial muscles or tongue except when he firmly innervates these muscles by retracting the corners of the mouth and protrudes the tongue when one sees a little exhaustability of innervation and a fine tremor which is not constant.

"The relative posture of the finger tips to the thumb is normal on each side, the finger spacing of the outstretched hands is symmetrical and the repeated thumb and forefinger apposition movement (diadokokinesia) is of normal amplitude in each hand. The pupils are quite wide in dilatation but symmetrical and react promptly to light and accommodation. The extra-ocular movements are full without nystagmus and convergence is done well. The eyegrounds are negative. Facial innervation is symmetrical and there is no bulbar weakness. The left biceps and triceps reflexes are more active than the right, the difference between the biceps being more marked than between the triceps. There is no Tromner reflex in either hand. The knee jerks are markedly exaggerated to the same degree, while the Achilles reflexes are moderately hyperactive but without clonus. The plantar and abdominal reflexes are normal, the latter markedly hyperactive, neither cremasteric reflex could be elicited. All forms of vital and gnostic sensations were tested and found intact throughout. The patient's speech is clearly enunciated, and there is not the slightest suggestion of dysrhythmia of articulation. He impresses me as being mentally alert, and there is nothing to suggest any deviation from the normal in the intellectual sphere.

"It would now appear that the acute striatal disturbance which was observed in the early part of May was due to perivascular edema rather than hemorrhage or an infiltrative tissue process, otherwise the disturbance would not have cleared up so completely in the short space of two weeks. The clinical course is a sound basis for a good prognosis, but one must make this with a certain reservation, namely, that there

is a possibility of the insidious development of Parkinsonism in the next year or two if only based on the experience with acute epidemic encephalitis'

IMMUNOLOGICAL STUDIES

(a) *Isolation of Virus* Efforts were made to recover the virus from both the spinal fluid and blood serum drawn after admission to the hospital prior to the administration of antiserum. Chick embryos and mice were injected with each fluid. Five 12-day chick embryos were each inoculated with 0.1 c.c. of blood serum and five with 0.1 c.c. of spinal fluid, three were inoculated with 0.5 c.c. each of blood serum and three with 0.5 c.c. each of spinal fluid. From a total of 16 embryos thus injected, one died. This embryo, which had received 0.1 c.c. of blood serum, died in less than 24 hours, and although no lesions characteristic of encephalomyelitis were apparent, the dead chick was ground finely with aluminum, the ground tissue then diluted with broth to 10 per cent suspension, and the supernatant fluid transferred to other embryos and mice. The embryos remained healthy and were discarded after a week. The mice were held for three weeks, no symptoms of encephalomyelitis were shown at any time.

Both the blood serum and the spinal fluid were each injected intracerebrally (0.03 c.c.) into five 21-day old Swiss mice. The mice were observed daily, no symptoms of encephalomyelitis developed. At the end of six weeks the animals were tested for susceptibility to the virus by injecting them intracerebrally with a dose of virus estimated as one lethal dose. In both sets of animals three out of five mice promptly developed encephalomyelitis and died at the same time as the controls. There was, therefore, no evidence that the animals had developed an immunity due to a subclinical infection.

(b) *Tests for Antiviral Neutralizing Antibodies* Specimens of blood serum and spinal fluid taken at various times during the patient's illness and period of recovery were studied for their antibody content. The specimens were kept frozen at -20°C and were tested at one time. The tests were made according to the intracerebral method of Cox and Olitsky⁶. Mixtures of equal volumes of blood serum or spinal fluid and virus dilutions were allowed to stand at 37°C for 45 minutes, after which they were injected intracerebrally (0.03 c.c.) into 21-day old Swiss mice. The description of the specimens tested and the results obtained are given in table 1. These tests were repeated three times with essentially the same results. In two tests, chick embryo propagated virus was used as a source of virus, in the third test, mouse brain passage was employed.

It is apparent that neither the spinal fluid nor the blood serum taken before the administration of antiencephalomyelitis serum contained definitely demonstrable antibodies. The results obtained with the blood serum suggest a trace of protection against one to 10 lethal doses of the virus, but in no one of the three tests made was the protection clear-cut. After the administration of very large doses of antiserum, both intravenously and intrathecally, antiviral immune substances were easily demonstrated in both blood serum and spinal fluid. This rise in antibody content can be entirely accounted for by the high potency of the antiserum employed. Tests showed that 0.015 c.c. of the antiserum neutralized 10,000 intracerebral mouse doses. It is interesting to note that the antibodies present in the spinal fluid as the result of the intraspinal and possibly the intravenous administration of antiserum disappeared within seven days.

TABLE I

Results of Tests for Neutralizing Antibodies to Encephalomyelitis Virus (Western Type) Iowa 1937 Strain, in Specimens of Spinal Fluid and Blood Serum
 Chick Embryo Passage No. 4 Used as Source of Virus Five Mice Injected Intracerebrally with 0.03 c.c. of Each Mixture

Specimen	Date Observed	Virus Dilutions										M L D s Protected Against
		10 ⁻¹	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻⁵	10 ⁻⁶	10 ⁻⁷	10 ⁻⁸			
Spinal fluid No 1 (specimen before antiserum)	4-26-39				3 4,5 5 5	4,5,5,6,6	4 4,5,6 6	5,5 5,5,5	S,S,S,S,S	1 (?)		
Spinal fluid No 2 (immediately after 550 cc antiserum were injected intravenously)	4-26-39				5,5,5,5,6	5,6,6 6 8	4,5 6,6 S	5 S,S,S,S	S S S S,S	1 (?)		
Spinal fluid No 3 (12 hrs after 550 cc and 50 cc of antiserum were injected intravenously and intraspinally respectively)	4-26-39				4 5,5 6,7	6,7,8,S S	Tr 1 Tr,S,S	S S,S,	S,S,S,S,S	10-100		
Spinal fluid No 4 (24 hrs after second intraspinal (50 cc) and intravenous (150 cc) injections of antiserum)	4-27-39				Tr,4,4 5,5	3 5 5,6,S	4,S,S,S,S	S S,S,S,S	S S S,S,S	10		
Spinal fluid No 5 (after additional injections of antiserum 4-27-39—150 cc intravenously, 1-28-39—100 cc intramusc, 1-29-39—50 cc intramusc)	5- 1-39				4 5,6,6 8	3,5,5 5,5 S	4,4,S,S,S	5,5 S,S,S	S S S S S	10		
Spinal fluid No 6	5- 3-39				3 3,4,4 4	3 4 5 5,6	5,5 9,S,S	S,S,S,S,S	S,S,S,S,S	1		
Standard antiserum control (western type)					S,S,S,S,S	S,S,S,S,S				10 000		
Virus controls (broth)					3 4,3 5 5	3,5,5 6 6	3,3,6 6 6	6,6,9,S,S	6 S S S S			
Blood serum No 1 (specimen before antiserum)	4-26-39				4,4,6 7 7	3 4 5 5 7	3,5,5 6 6	4,6 6 S S		1-10 (?)		
Blood serum No 2 (immediately after antiserum) See spinal fluid No 2	4-26-39				4 5 5 7 7	5 6,7 S S	S S S S,S	S,S S S S		100 +		
Blood serum No 3 (see spinal fluids No 3 and No 4)	4-27-39				4 4 4 4 5	5 5 5,S S	S S,S,S,S	S,S S S S		100 +		
Blood serum No 4 (1 mo. after onset of disease)	8-23-39	S S S, S S	S S S, S S	6 S S, S S	S S S S,S	8 S S S S	7 S S S S	S S S S,S		10 000,000 +		
Standard antiserum control (western type)		5 8 9 11 S	6 7,7 7 7	5 5 5 S S	8 S S S S	5 S S S S				10 000		
Virus controls (broth)					3 3 4,4 4	3 3 4 4 4	3 4 4 5 7	4 4 5 5 10	4 5 7 S S			

* Figures indicate day of death of each mouse † S indicates survival for ten days ‡ Tr indicates death from trauma

After recovery and four months after onset of illness, 0.015 cc of the patient's blood serum neutralized at least a million lethal doses of the virus. The demonstration of this high titer after recovery in contrast to the questionable presence of antibodies at the onset of the disease offers sufficient evidence as to its etiology in spite of our failure to recover the virus from the spinal fluid or blood. A specimen of blood drawn eight months after the onset of the disease (December 12, 1939) also protected mice against 1,000,000 lethal doses of virus. A specimen of blood taken four months later (April 24, 1940) still contained neutralizing antibodies. Though its titer had dropped, it protected mice against 10,000 lethal doses of virus.

Tests made on two specimens of blood serum taken after recovery failed to protect against a single lethal dose of the Eastern type of virus.

FOLLOW-UP

The patient returned to work on July 5, 1939, when he was assigned to a different department. He was seen by one of us (H. G.) on July 16, 1939, when he had regained his normal weight (127 lbs). Appearance was normal. No staring. There was a slow steady tremor of the lids. There was also a coarse tremor of the tongue on extension. Gait was normal except that the left arm did not swing as much as the right. There was no difficulty in walking except that, when tired, the patient was forced to stamp the left foot. Otherwise it was normal. The deep reflexes were prompt and equal. Abdominal reflexes were normal. Could not elicit the cremasteric reflexes. Patient stated that in the last two weeks he noted a diffuse loss of hair. Still taking Vitamin B complex capsules (4 a day).

He was examined again on May 25, 1940. Weight was 127½ lbs. There were no complaints. Memory and powers of concentration were good. The sensation of stamping of the left foot had disappeared. Played golf well, without undue fatigue. Hair growth was normal. Frequent winking was noted. On closing the lids a fine regular tremor occurred (the patient was not conscious of the winking although his girl friend had drawn his attention to it and asked him to stop it). Pupils were in mid-position, equal and reacted to light and accommodation. There was a coarse tremor on extreme protrusion of the tongue. The patient smiled well and the expression was normal, but on forced contraction of the mouth there was noted some quivering of the muscles of the chin and lower lip. The biceps reflexes were more active on the right, the triceps were normal, and the knee jerks were hyperactive, but equal. Upper abdominal reflexes were exaggerated while the left lower abdominal and cremasteric reflexes were absent. Muscle tone was normal throughout the body. Romberg and Babinski tests were negative. Finger to nose test and apposition movements were normal although he tired rather easily. There was a slight tremor of the left hand. Gait was normal. Libido was normal.

A final neurological reexamination was done by Dr. A. M. Ornstein on July 31, 1940, who reported the following:

"The mild reflex changes and left-sided associated movement defect found a year ago have entirely disappeared. The station and gait are normal, both arms move actively in their normal associated movements with the lower limbs. His station is secure in the Romberg position, there is no fluttering of the eyelids, his extended hands show no tremor of the finger tips, and he performs the finger-to-nose test equally well on the two sides.

"There is a tendency for the left pupil to be slightly larger than the right in a subdued light, but the difference is not noticeable in a well-lighted room. Both pupils react promptly to light and accommodation. The extra-ocular movements are full

without nystagmus and the eyegrounds are normal. Facial innervation is full and symmetrical, the tongue protrudes in the mid-line without tremor, and the retracted corners of the mouth remain equally retracted without fatigability on either side or tremor of the perioral muscles. The soft palate is normally innervated, facial sensation is normal and the corneal reflexes are active.

"The tone of the musculature of the upper and lower limbs is normal and equal on the two sides of the body, there not being the slightest suggestion of extrapyramidal cogwheel tension in the left upper limb, the extremity which was originally predominantly involved. The posture of the fingers is normal and he executes perfectly rapid alternating movements with the fingers of each hand. The tendon reflexes at the elbows are bilaterally hyperactive in a moderate degree but equally so, there is no Trommer reflex in either hand. The knee and ankle jerks are quite hyperactive but to the same degree in each limb. The abdominal reflexes are exceedingly hyperactive, both the upper and lower, the cremasteric reflexes could barely be obtained, both plantar reflexes are of the normal flexor type. All forms of vital and gnostic sensation were found intact throughout. The patient is mentally alert and his speech is normal.

"Subjectively J. R. is perfectly normal and says that the occasional headache he has is no more than he had prior to his serious illness of last year. He has had no recurrence of any of the cerebral symptoms which complicated his acute ailment. It can be safely stated that he has no residual signs of his former organic brain disease and there is nothing to suggest a beginning late extra-pyramidal symptom-complex such as often complicates epidemic encephalitis. Last year I reported a moderate hyperactivity of the left-sided reflexes as compared to the right, this is not in evidence today. The absent cremasteric reflexes at that time were associated with hyperactive abdominal reflexes, and the same is noted today. I do not consider this of importance. The fine tremor of the lips and the fluttering of the closed eyelids reported then are absent today."

SUMMARY

The clinical record and follow-up observations of a laboratory infection with encephalomyelitis virus (Western type) are here presented. Although the virus was not recovered from the patient's blood or spinal fluid, the appearance in the blood of specific neutralizing antibodies in extremely high titer after recovery (when passive immunity is out of the question) in contrast to the doubtful presence of immune substances at the onset of the disease constitutes convincing laboratory proof of the etiological agent involved. Large quantities of a highly potent immune horse serum were administered intravenously and intrathecally. Acute Parkinsonism developed at the end of the second week of the disease when signs of infection had subsided. At that time the patient was suffering from serum sickness. Complete recovery occurred.

ADDENDUM

Since this report was submitted for publication Zichis and Shaughnessy (Jr. *Am. Med. Assoc.*, 1940, cxv, 107) have presented interesting experimental evidence concerning the therapeutic value of large doses of highly potent immune rabbit serum in the treatment of experimentally induced Western equine encephalomyelitis in guinea pigs and mice. This is in line with the clinical impression obtained from our case.

We wish to thank Drs. LeRoy Wenger, H. B. Conaway, S. F. Gilpin, and A. M. Ornstein of Philadelphia for the clinical notes they made on this case.

REFERENCES

- 1 MEYER, K F A summary of recent studies on equine encephalomyelitis, *Ann Int Med*, 1932, *vi*, 645
- 2 FOTHERGILL, L D Equine encephalomyelitis Virus and rickettsial diseases, Harvard School of Public Health Symposium (1939), 1940, Harvard University Press, Cambridge, Massachusetts, p 661
- 3 OLITSKY, P K Infection with equine encephalomyelitis virus Practice of Pediatrics (J BRUNNEMAN), W F Prior Company, Hagerstown, Maryland, Volume IV, Chapter VII, Section 2, 1938
- 4 FOTHERGILL, L D, HOLDEN, M, and WICKOFF, R W G Western equine encephalomyelitis in a laboratory worker, *Jt Am Med Assoc*, 1939, *ciii*, 206
- 5 GORDON, J E Epidemiologic problems of virus disease Virus and rickettsial diseases Harvard School of Public Health Symposium (1939), 1940, Harvard University Press, Cambridge, Massachusetts, p 53
- 6 COX, H R, and OLITSKY, P K Active immunization of guinea pigs with the virus of equine encephalomyelitis III Quantitative studies of serum antiviral bodies in animals immunized with active and inactive virus, *Jr Exper Med*, 1936, *liiv*, 217

NON-ICTERIC LEPTOSPIROSIS ICTEROHEMORRHAGIA (WEIL'S DISEASE) CONTRACTED WHILE BATHING *

By PERK LEE DAVIS, M D, F A C P, *Philadelphia, Pennsylvania*, and
MARGARET SHUMWAY DAVIS, M D, *Gladwyn, Pennsylvania*

BECAUSE the term Weil's disease is usually associated with a severe infection with jaundice and bleeding, it is possible that the correct diagnosis of cases without these features is seldom made. According to several opinions jaundice is said to be present in about 50 per cent of cases, but it is probable that if all mild cases were recognized the proportion would be much lower. Jaundice and bleeding are characteristic of the severe infections. Since a clinical diagnosis can not be made in the mild form, it is necessary to apply various biologic tests. It is important, of course, that the mild as well as severe cases be recognized.

Studies elsewhere in the world, especially in Europe and in the East Indies, show that numerous other varieties of leptospira may cause infection similar to Weil's disease in which jaundice is reported in less than 5 per cent of cases. The subject was recently reviewed by Havens, Bucher and Reimann.¹

Infection with leptospiroses during bathing or submersion in water contaminated with the excreta of rats, the common source of the disease, has long been recognized, but only recently have out-breaks been recorded in this country.¹ The following report describes a case contracted in this manner.

CASE REPORT

On September 3, 1938, a man, aged 25, swam in a quarry pond. Rats were seen running about the adjacent rocks. Nine days later he was taken with severe cramps in the abdomen, diarrhea, intense headache, pains in the back and legs, and fever of

* Received for publication March 24, 1941

103.4° F The pulse rate was 126 per minute, the blood pressure 90 millimeters of mercury systolic and 60 diastolic. The conjunctivae soon became deeply injected and a subconjunctival hemorrhage appeared in the left eye. There was no jaundice. The pharynx appeared to be deep red and plush-like, the liver and spleen became enlarged and tender, and the cecum was distended. Peristalsis was greatly increased and signs of meningismus developed.

The erythrocytes on the third day of the disease numbered 3,700,000 per cubic millimeter of blood, the leukocytes 15,000, of which 59 per cent were polymorphonuclear cells, 24 per cent lymphocytes, 8 per cent monocytes, 7 per cent eosinophile cells and 2 per cent basophiles. The hemoglobin measured 60 per cent (Sahli). The urine contained albumin and erythrocytes, the specific gravity was 1.035. Agglutinins for *Leptospira icterohemorrhagiae* were absent during the disease. The icterus index was 7 and 8 units on two occasions. Dark field study of both blood and urine at intervals failed to reveal leptospiras. On the fourth day of the disease five cubic centimeters of the patient's blood were injected intraperitoneally into each of two guinea pigs. On the eighth day five cubic centimeters of the patient's urine were injected intraperitoneally into two more guinea pigs. The first two animals died seven and eight days after inoculation, the latter two died 10 and 12 days after inoculation respectively. All four guinea pigs were studied post mortem. There was general icterus of the tissues, and there were hemorrhages in the lungs, intestines and kidneys. Leptospiras were found in the liver on microscopic examination. Samples of water were then obtained from the pond in which the patient swam, one gallon was taken from the edge and one gallon from the middle of the pond. These specimens were concentrated by centrifugation and the sediment injected intraperitoneally into guinea pigs. No evidence of infection appeared.

The patient was given daily intravenous injections of 200 c.c. of 10 per cent solution of glucose. Codeine sulfate was used liberally to relieve pain. The fever gradually returned to a normal level after eight days, only to rise suddenly to 38.9° C (102° F) three days later. The fever continued for another five days when it began to fall, it reached normal after four days. Asthenia persisted for two months.

SUMMARY

A man aged 25 contracted non-icteric leptospirosis while bathing in water polluted by rats. It is of importance to bear in mind the danger of infection with these microorganisms when bathing in quiet water likely to be contaminated with the excreta of these rodents.

BIBLIOGRAPHY

1. HAWINS, W. P., BUCHER, C. J., and REIMANN, H. A. Leptospirosis a public health hazard, Jr. Am. Med. Assoc., 1941, cxvi, 289-291.

**VENTRICULAR FIBRILLATION IN ACUTE CORONARY
ARTERY THROMBOSIS DURING THE INTRAVENOUS
ADMINISTRATION OF QUINIDINE SULPHATE;
REPORT OF A FATAL CASE***

By HAROLD L. RAKOV, M.D., *Kingston, New York*

INTRODUCTION

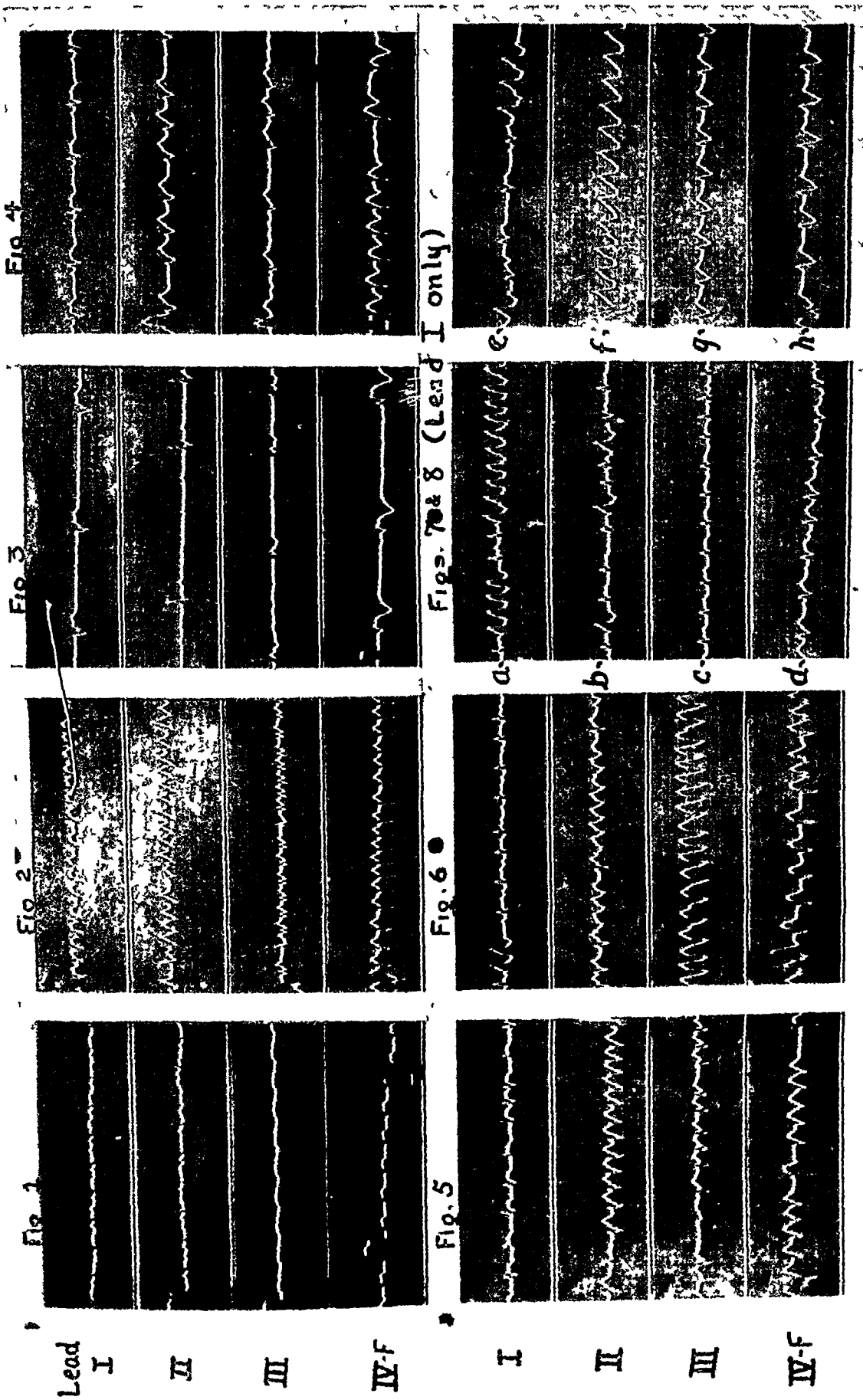
THE ectopic rhythms which occur following an acute myocardial infarction are usually transitory and benign. Sometimes ventricular tachycardia is an exception to this rule. This arrhythmia has been produced experimentally by ligation of the coronary arteries, and Levine¹ observed it frequently in acute myocardial infarction. Master,² on the other hand, found that it occurred in coronary occlusion infrequently except following the use of digitalis. The ischemic area is hyperirritable and a source of this idioventricular rhythm. Epinephrine enhances this irritability not only by increasing the myocardial ischemia at a time when a greater blood supply is needed,³ but also because its direct toxic effect further accentuates the excitability of the myocardium. Wiggeis⁴ believes that the use of this stimulating drug cannot be expected to benefit an anoxic mammalian heart and that it usually sets up multiple ventricular pace makers. Further, anything that depresses the normal regulatory function of the Tawara-His Purkinje system on the ventricular myocardium, as quinidine, may precipitate this rhythm. Smith et al.⁵ proved experimentally in dogs that after the intravenous administration of quinidine sulphate and subsequent coronary artery ligation the myocardium is more sensitive to the establishment of ectopic foci, and conclude that this drug is of little use in the preventive treatment of ventricular tachycardia or ventricular fibrillation.

It is highly probable that the administration of adrenalin brought about ventricular tachycardia in the following case, and that the subsequent use of quinidine led to ventricular fibrillation and death.

CASE REPORT

M. M., a robust 57-year-old white male, had been free from any evidence of heart disease until 36 hours before admission to the Kingston Hospital on the afternoon of July 20, 1940. At that time, while performing an unusually arduous task, he was suddenly seized with a severe crushing pain in the interscapular area radiating anteriorly to the epigastrium, accompanied by nausea, vomiting and, later, slight dyspnea. Dr. H. Keator of Kingston, New York, instituted the usual therapeutic procedures for acute coronary occlusion, but because of persistent vomiting, glycosuria and acetonuria, hospitalization was advised. Shortly after admission to the hospital, the patient was in no great distress but complained of nausea and dull pain in the interscapular area radiating anteriorly to the sternum and down both arms. Dyspnea was not marked, but there was slight cyanosis. Upon examining the fundi, slight arteriosclerotic changes in the retinal arteries were noted, but there were no hemorrhagic or atrophic areas. The blood pressure was 98 mm Hg systolic and 64-60 mm diastolic, and the pulse was regular with a rate of 94. A localized pericardial friction rub of mild intensity was heard over the left sternal border, and the heart sounds had an

* Received for publication January 7, 1941



embryocardial quality. A few crepitant râles were heard at the base of the right lung, but there was no enlargement of the liver, nor was there peripheral edema. The electrocardiogram (figure 1) revealed normal sinus rhythm with evidence of a recent myocardial infarct of the anterior pattern. Chemical analysis of the urine showed marked glycosuria and acetonuria, but the microscopic examination was essentially negative. Blood studies revealed 275 mg of sugar per 100 c.c. of blood, a carbon dioxide combining power of 54 volumes per cent, 5,950,000 erythrocytes per cu. mm., with 108 per cent of hemoglobin (156 gm = 100 per cent), and 22,100 leukocytes per cu. mm., 88 per cent of which were polymorphonuclears. Subsequent determinations of blood sugar and carbon dioxide combining power varied only slightly from the above.

It was concluded that we were dealing with an acute myocardial infarct in an individual with previous asymptomatic diffuse vascular disease involving the coronary arteries. The glycosuria and hyperglycemia often observed in coronary thrombosis were doubtless due in part to the diffuse vascular disease and in part to a compensatory physiological response of the body. The acetonuria was probably caused by persistent vomiting with dehydration and was not accompanied by ketosis. Fluids were given parenterally, but insulin was not indicated.

Under the usual régime of bed rest, morphine and oxygen, the patient was quite comfortable until the next morning when, because of slight increase in dyspnea, unaccompanied by any change in the character of the pulse, an intern gave 15 minims of adrenalin. Shortly thereafter the patient became semicomatose and Cheyne-Stokes respirations, nausea, vomiting and cyanosis, together with a precipitous drop in blood pressure were noted. The heart beat at the apex was rapid, slightly irregular, and the varying intensity of sounds suggested paroxysmal ventricular tachycardia. This was confirmed by electrocardiographic studies (figure 2).

Seven grains of quinidine sulphate in 70 c.c. of normal saline (as advised by Hepburn and Rykert⁶) were then given intravenously over a period of 35 minutes, when a classical Stokes-Adams syndrome ensued and an electrocardiogram revealed complete A-V dissociation (figure 3). However, within 10 minutes normal sinus rhythm was established followed by frequent interpolations of ventricular extrasystoles (figure 4). Concomitantly, the patient roused from his comatose state, cyanosis disappeared, respirations became easier, and the blood pressure rose. On the following day, because of persistent premature ventricular beats (figure 5), a total of 20 grains of quinidine sulphate was administered orally in divided doses over a period of 16 hours. The patient against became semi-moribund, cyanotic and dyspneic, and the electrocardiogram (figure 6) revealed rather prolonged and frequent paroxysms of

FIG 1 Electrocardiogram taken on admission at 1 00 p.m., July 20, 1940, showing evidence of acute myocardial infarction of anterior pattern, with normal sinus rhythm.

FIG 2 Electrocardiogram, 10 30 a.m., July 21, 1940, following the administration of 1 c.c. adrenalin showing ventricular tachycardia.

FIG 3 Electrocardiogram, 11 05 a.m., July 21, 1940, following administration of seven grains of quinidine sulphate intravenously, showing complete auricular ventricular dissociation.

FIG 4 Electrocardiogram 10 minutes after the discontinuance of intravenous quinidine as in figure 3, showing return to normal sinus rhythm followed by paroxysms of ventricular tachycardia.

FIG 5 Electrocardiogram at 11 00 a.m., July 22, 1940, showing persistence of paroxysms of ventricular tachycardia.

FIG 6 Electrocardiogram at 10 30 a.m., July 23, 1940, still showing persistence of paroxysms of ventricular tachycardia in spite of oral quinidine therapy.

FIGS 7 and 8 Series of electrocardiograms in Lead I, during the intravenous administration of five grains of quinidine sulphate, started at 11 25 a.m. and continued over a period of 30 minutes, showing a transition from ventricular tachycardia to ventricular fibrillation. a—11 30 a.m., b—11 40 a.m., c—11 45 a.m., d—11 50 a.m., e—11 52 a.m., f—11 55 a.m. (quinidine discontinued), g—11 58 a.m., h—12 03 p.m.

ventricular tachycardia. Intravenous quinidine was again resorted to, and over a period of 30 minutes 50 c.c. of the previously mentioned solution had been administered, when the patient gave a loud maniacal shriek, threw his arms and legs wildly about, attempted to jump out of bed and within 30 seconds collapsed. An almost continuous electrocardiogram in Lead I (figures 7 and 8) during this period of 30 minutes showed premature ventricular beats arising in multiple foci, paroxysms of ventricular tachycardia and, finally, ventricular fibrillation. After respirations had ceased and heart sounds became inaudible the electrocardiogram recorded actively for six minutes. Artificial respiration and the intravenous administration of coramine and caffeine sodium benzoate were of no avail, and finally adrenalin was given intracardially without benefit.

DISCUSSION

It has been reported that ventricular tachycardia complicating acute coronary artery thrombosis can be abolished by the use of quinidine, and now it is universally believed that the drug may control this purposeless, inefficient rhythm. Quinidine will alleviate the symptoms of heart failure in such instances only in so far as it can slow the rate without diminishing the force of the heart beat. However, the drug, by its toxic action, may not only fail to slow the rate by restoring normal sinus rhythm but on the contrary may bring about ventricular fibrillation.

The favorable results reported by Hepburn and Rykert⁶ with an average intravenous dose of 20 grains of quinidine have stimulated indiscriminate employment of this drug. But it is not clear how many of their series of nine cases were associated with recent myocardial infarction, and, strangely enough, their only immediate adverse, almost fatal result occurred with only nine grains of quinidine in an individual who developed ventricular tachycardia two weeks after an attack of coronary thrombosis.

Levine and Fulton,¹ in their series of eight cases of ventricular tachycardia following acute coronary thrombosis, noted a return to normal sinus rhythm following administration of either oral or intravenous quinidine. It is difficult to be certain what part the quinidine played in producing these results. It is worthy of note that six of the eight cases died within two weeks, a high mortality rate indeed for acute myocardial infarction. Apparently the basic disease process which ultimately decides the outcome in myocardial infarction can be adversely influenced by quinidine. The ectopic rhythms associated with acute myocardial infarctions are usually transient and generally revert to normal sinus rhythm with no specific medication.

Stopping this so-called circus movement is dependent upon the predominant ability of quinidine to shorten the responsive gap by prolonging the refractory period over its accompanying effect in diminishing the rate of conduction of the impulse. These effects are predominantly on the ventricular muscle, and to a less extent on the junctional tissues. Occasionally a more significant effect can be exerted on a vulnerable diseased His-Purkinje system depressing A-V conduction and precipitating ventricular fibrillation. Schwartz and Jezer⁷ produced transient ventricular fibrillation in two patients with A-V dissociation by intravenous quinidine, and Sprague and Davis⁸ reported a fatality with ventricular fibrillation and A-V dissociation in the course of quinidine therapy in an individual with an already depressed atrioventricular conduction system caused by previous digitalis

medication. Often following coronary occlusion impaired function of the His-Purkinje system may be latent, or else so slight and transient as to escape detection even by the electrocardiogram. This was probably true in our case since 7 grams of intravenous quinidine would not produce complete A-V dissociation in the absence of previous damage of the conduction system. Thus the patient had a perfect set-up for ventricular fibrillation, i.e., a hyper-irritable ventricular focus plus an impaired A-V conduction system. Quinidine further depressed the conduction mechanism to provoke this fatal rhythm.

Since it is frequently impossible to predetermine the presence of disease of the bundle tissues, the routine prophylactic administration of quinidine following acute coronary artery occlusion will always be a potentially hazardous procedure. There has not been sufficient evidence to substantiate the premise that quinidine may prevent sudden death from ventricular fibrillation following acute myocardial infarction. On the contrary, the drug under these conditions may become a powerful noxious agent and, as in this case, enhance the development of the fatal rhythm it was intended to forestall. Only when the acute myocardial reaction has subsided are we justified in risking quinidine, for then there is not present the marked myocardial irritability of the acutely infarcted area and we can reasonably accept electrocardiographic evidence of absence of conduction defects as indicating a healthy conduction system. In the above case the drug not only incited, but also perpetuated a malignant circus movement in a heart muscle made susceptible by occult involvement of the A-V conduction system.

The immediate terminal mechanism in quinidine intoxication is apparently controversial. Levine⁹ showed experimentally in cats that the immediate cause of death from quinidine was a marked central depression of the respiratory mechanism, and that the heart continued to beat for two minutes after complete respiratory failure without evidence of ventricular fibrillation in most of the cases. Smith¹⁰ believes the immediate cause of death to be cardiac standstill due to depression of both S-A and A-V nodes. However, Davis and Sprague in their fatal case observed evidence of circus movements in the ventricle of the nature of fibrillation, accompanied by auricular standstill, and the cardiac action continued for several minutes after signs of life were absent. In our case ventricular fibrillation was the terminal mechanism and persisted for six minutes after all clinical signs of life were absent.

CONCLUSION

A case of sudden death during the intravenous administration of quinidine sulphate for ventricular tachycardia following acute myocardial infarction is reported. The mechanism of death as recorded electrocardiographically was ventricular fibrillation.

REFERENCES

- 1 LEVINE, S. A., and FULTON, M. H. Effect of quinidine sulphate on ventricular tachycardia—clinical observations, *Jr Am Med Assoc*, 1929, **LVII**, 1162.
- 2 MASTER, A. M., DACK, SIMON and JAFFE, H. L. Partial and complete heart block, *Am Jr Med Sci*, 1938, **CXCVI**, 513.
- 3 MILLES, GEORGE, and SMITH, PAUL W. Effects of epinephrin on the heart, *Am Heart Jr*, 1937, **XIV**, 198.

- 4 WIGGERS, CARL J The mechanism and nature of ventricular fibrillation, *Am Heart Jr*, 1940, xx, 399
- 5 SMITH, F H, McEACHERN, C G, and HALL, G E The effect of the intravenous administration of quinidine sulphate on the development of ventricular fibrillation following sudden occlusion of the circumflex branch of the left coronary artery—an experimental study, *Am Heart Jr*, 1940, xx, 620
- 6 HEPBURN, JOHN, and RYKFRT, H E Use of quinidine sulphate intravenously in ventricular tachycardia, *Am Heart Jr*, 1937, xiv, 620
- 7 SCHWARTZ, SIDNEY B, and JEZER, ABRAHAM The action of quinine and quinidine on patients with transient ventricular fibrillation, *Am Heart Jr*, 1934, ix, 792
- 8 DAVIS, DAVID, and SPRAGUE, HOWARD B Ventricular fibrillation—its relation to heart block, report of a case in which syncopal attacks and death occurred in the course of quinidine therapy, *Am Heart Jr*, 1929, iv, 559
- 9 GORDON, BURGESS, MATTON, MARCEL, and LEVINE, S A The mechanism of death from quinidine and a method of resuscitation, an experimental study, *Jr Clin Invest*, 1925, i, 497
- 10 SMITH, H L, and BOLAND, E W Treatment of auricular fibrillation with quinidine and strychnine, *Jr Am Med Assoc*, 1939, cxiii, 1017

EDITORIAL

THE RELATION OF SPECIFIC IMMUNITY TO RECOVERY FROM PNEUMOCOCCUS PNEUMONIA TREATED WITH THE SULFONAMIDES

THE remarkably successful results obtained clinically in the treatment of pneumococcus pneumonia with the sulfonamide drugs have stimulated interest in the mechanism of their action, and in their influence on the development of immunity to this organism

Earlier studies by Whitby¹ and others of the effect of sulfapyridine on pneumococci in vitro showed that in concentrations such as can be obtained in the animal body, it exerts a bacteriostatic effect, inhibiting the growth of the organisms without actually destroying them. In higher concentrations an actual bactericidal action may be manifested. This action is not exerted immediately. In a freshly inoculated culture containing the drug in effective concentration, there is active multiplication, which at first is equal to that in the controls. It is only after about six hours that multiplication is inhibited^{2,3}. It is evident, therefore, that the action of the drug is not that of a simple germicide, but that it interferes with growth in some more subtle way. McIntosh and Whitby² among others have suggested that it may block the action of some bacterial enzyme. The exact mechanism of its action is not yet settled.

In the animal body the drug behaves in a similar manner². Thus in the peritoneum of a mouse—even if an effective dose of sulfapyridine has been previously administered—pneumococci multiply actively for a few hours and penetrate into and begin to multiply in the blood stream. Then the inhibitory effect of the drug comes into play, and after 24 hours organisms may no longer be demonstrable. In this respect sulfapyridine differs sharply from immune serum in its action, for the latter exerts its effect immediately.

The inhibitory effect of the drug and the arrest of the infectious process is not accompanied by the immediate appearance of phagocytosis, or of other evidences of antibody production. If the drug is stopped prematurely, there may be a flare-up of the infection. If the administration of the drug is continued and the mice survive, after a few days antibodies do appear, and the mice are found to have a substantial active immunity to reinfection. This immunity is specific and limited to the type of pneumococcus with which the mice were originally infected. Whitby found it to be substantially identical in degree with that produced by inoculating mice with a similar quantity of heat-killed pneumococci. The administration of sulfapyridine to

¹ WHITBY, L. E. H. Chemotherapy of pneumococcal and other infections with 2 (p-amino-benzenesulfonamido) pyridine, *Lancet*, 1938, i, 1210-1212.

² MCINTOSH, J., and WHITBY, L. E. The mode of action of drugs of the sulfonamide group. *Lancet*, 1939, i, 431-435.

³ SPRING, W. C., LOWELL, F. C., and FINLAND, M. Studies on the action of sulfapyridine on pneumococci, *Ir. Clin. Invest.*, 1940, vi, 163-177.

these vaccinated mice did not affect the speed of development or degree of immunity produced

It seems probable, therefore, that in the mouse sulfapyridine does not directly kill the organisms, but that it inhibits their growth until the natural defensive forces can come into play. The pneumococci are then eliminated, probably in large measure by phagocytosis.

It has long been recognized that in man specific antibodies appear in the blood in most cases at about the time of spontaneous recovery from pneumonia, on or near the sixth day. It is believed that recovery is brought about by the activity of these substances, particularly by phagocytosis. The aim of treatment by immune serum has been to supply such substances in larger quantity and at an earlier stage of the infection than the patient himself can produce them. There has been doubt, however, as to the part this natural immune mechanism plays in the recovery of patients treated with sulfapyridine.

Patients with lobar pneumonia who are given adequate doses of sulfapyridine early in the disease often show a fall in temperature within 36 hours. At this time, however, there is usually no evidence of antibody formation in the serum. If sulfapyridine is continued, antibodies usually appear a few days later, at about the time their appearance would be expected in patients recovering spontaneously.^{4,5} The sulfapyridine does not demonstrably influence the development of the immune response. The same phenomena have been observed after treatment with sulfathiazole and sulfadiazine.⁶

If administration of sulfapyridine is stopped prematurely in such cases, soon after the temperature has fallen and when no antibodies are demonstrable, there is often a secondary rise in temperature and flare-up of the infection a day or two later, after the drug has been eliminated. In the absence of complications, however, such a relapse rarely occurs if the drug is continued until there has been time for antibodies to develop. This led Wood and Long⁴ to suggest that the slow development of antibodies explains these relapses following premature discontinuance of the drug.

If permanent recovery is dependent upon the natural immunity mechanism, it should be possible usually to demonstrate antibodies in the blood. The frequency with which they have been found has varied considerably, depending probably upon the methods used. Thus Kneeland and Muliken,⁷ testing for precipitins, found only four positive out of 19 cases treated with sulfapyridine and 16 positive out of 21 cases treated with sulfathiazole.

⁴ Wood, W. B., and Long, P. H. Observations upon the experimental and clinical use of sulfapyridine. III. The mechanism of recovery from pneumococcal pneumonia in patients treated with sulfapyridine, *Ann Int Med*, 1939, **xiii**, 612-617.

⁵ Finland, M., Seeling, W. C., and Lowell, F. C. Immunological studies on patients with pneumococcal pneumonia treated with sulfapyridine, *Jr Clin Invest*, 1940, **xix**, 179-198.

⁶ Finland, M., et al. Sulfadiazine: therapeutic evaluation and toxic effects on 446 patients, *Jr Am Med Assoc*, 1941, **cxvi**, 2641-2647.

⁷ Kneeland, Y., and Muliken, B. Antibody formation in cases of lobar pneumonia treated with sulfapyridine, *Jr Clin Invest*, 1940, **xix**, 307-312.

Other observers,⁷ as already noted, have found them more regularly by utilizing other methods, especially agglutination or mouse protection tests. Fox et al.⁸ found eventually a strongly positive agglutination test (Sabin method) in 133 out of 144 cases recovering under sulfapyridine treatment. They found Francis' skin test less reliable, as did Haviland⁹ in cases receiving sulfapyridine and small doses of serum. Failure to demonstrate antibodies uniformly is not necessarily significant, as this is not always possible in cases recovering spontaneously. This might be owing to lack of sensitiveness of the methods available. Furthermore, the antibodies in the serum represent excess production, and it is quite conceivable that recovery might occur with a production of antibodies so meager as to leave no demonstrable excess in the circulating blood.

The delay in the appearance of antibodies (after apparent recovery) in patients treated with sulfonamide drugs has raised the question as to whether the drugs delay or inhibit the development of active immunity. This is difficult to determine directly in man, but the available evidence tends to show that the drugs neither hinder nor accelerate the process. Recently Curnen and McLeod¹⁰ have tested this point in rabbits. The animals were given a single dose of killed Type 1 vaccine, and half of the group was given sulfapyridine by mouth, during the period of developing immunity. The drug was then stopped and the presence of active immunity was determined by giving at varying intervals intracutaneous inoculations of living culture by Goodner's method. The immunity in the group which had received sulfapyridine was identical with that in the rabbits which had not received it.

If we accept the view that final recovery depends upon the activity of the immune mechanism of the individual and that sulfapyridine merely inhibits multiplication of pneumococci until this can develop, one would expect that the early supplementary administration of immune serum would be beneficial in accelerating recovery and presumably lessening mortality. Some basis for such an assumption may be found in animal experiments. If the dosage of inoculum, drug and immune serum is properly adjusted, mice can be protected by a combination of drug and serum, whereas neither drug nor serum alone would be effective.⁹ Probably some summation of their effects might be obtained in man, at least in occasional individual cases. However, this appears to be exceptional, since in the largest and most carefully controlled series of cases, the supplementary administration of serum has not reduced the mortality below that in cases treated only with sulfonamide drugs. Thus Plummer et al.,¹¹ in a study of 607 cases, reported a mortality of 9.8 per cent.

⁸ FOX, W. W., ROSI, R., and WINTERS, W. L. The Sabin agglutination test and the polysaccharide skin test (Francis) as indices of recovery in pneumonia, *Am. Jr. Med. Sci.*, 1940, cc, 649-655.

⁹ HAVILAND, J. W. Type 1 pneumococcal pneumonia. Clinico-immunological studies with special reference to the rationale of combined serum and drug therapy, *Bull. Johns Hopkins Hosp.*, 1941, lxxviii, 32-50.

¹⁰ CURNEN, E. C., and McLEOD, C. M. The effect of sulfapyridine upon the development of immunity to pneumococcus in rabbits, *Jr. Exper. Med.*, 1942, lxxv, 77-92.

¹¹ PLUMMER, N., ET AL. Chemotherapy versus combined chemotherapy and serum, *Jr. Am. Med. Assoc.*, 1941, cxvi, 2366-2371.

in patients receiving drug and serum, and 9.3 per cent in cases receiving drug alone (Cases dying in less than 24 hours were excluded from both groups). Immune serum, if available, should be given to patients who show toxic reactions to sulfonamide drugs or who fail to respond to them in the usual way, since it is known that drug-fast strains exist. However, these observations raise doubt as to the need or advisability of combining serum with sulfonamide drugs as a routine procedure. Further study will be required to determine whether there is any advantage in doing so.

Some attempts have been made to utilize the appearance of antibodies as an indication that treatment with the sulfonamides has been adequate. Francis' skin test, which is quite useful in controlling treatment with immune serum, is said to be unsatisfactory. Fox⁸ has recommended the Sabin agglutination test as an indication of effective immunity and believes that a strongly positive reaction warrants discontinuing the drug if the patient has made satisfactory clinical improvement and if complications can be excluded. Other investigators, however, have reported some degree of agglutinating power in the serum of patients who have later died of the disease, and further work will be necessary to determine the dependability of the test.

P. C.

BOOK REVIEWS

Management of the Cardiac Patient By WILLIAM G. LEAMAN, JR., M.D., F.A.C.P.,
Assistant Professor of Medicine in charge of the Department of Cardiology,
Woman's Medical College of Pennsylvania 705 pages, 23.5 × 16 cm J. B.
Lippincott Co., Philadelphia 1940 Price, \$6.50

This volume has been written with the practitioner and his problems especially in mind. Although dealing primarily with the treatment of heart disease, it offers a briefer discussion of disease entities, methods of diagnosis including electrocardiography and roentgenographic methods, and instructions regarding the performance and interpretation of certain tests, such as the determination of the venous pressure and the measurement of circulation time, etc. The author makes a feature of the presentation of many illustrative cases, with their management and a discussion of what was accomplished. Specific instructions are given in regard to carrying out such procedures as thoracentesis and abdominal paracentesis. One notes the following statement: "Following abdominal paracentesis, it is a good practice to keep the patient in bed until the next day." In heart disease, when abdominal paracentesis is necessary, this seems to be something of an understatement, unless further explanation be given. Some may wonder at the classification of a patient with a blood pressure of 120/90 as hypertensive—no further comment is made on the blood pressure in this patient, and no further recordings are presented.

The most valuable part of this volume is the presentation of the case histories with notes as to the management of the patients concerned, and frank discussion of the results obtained and the diagnostic problems. It should be of considerable help to the busy practitioner who can find similarities between his case problems and those here presented.

W. S. L., JR.

The March of Medicine Number VI of the New York Academy of Medicine Lectures to the Laity. Introduction by HAVEN EMERSON, M.D. 154 pages, 21 × 14 cm. Columbia University Press, New York 1941. Price, \$2.00.

Like its predecessors in this series, "The March of Medicine," 1941, maintains a high standard of informative material about certain fields of medicine addressed to the laity. The introduction states: "Earlier series have related the systematic progress in conquest of disease, the methods by which physicians become indispensable experts in human salvaging. Here are offered some fruits of contemplation, of reasoned delving into the causes and results of ancient events and almost traditional iconoclasm, and with but one exception all contribute to the pressing preoccupation of the much confused man of today." This series is rather deeper, more philosophical and more difficult to read than the previous series, however, it is also more thought-provoking. To the writer, the most entertaining and interesting lecture is "Paracelsus in the Light of Four Hundred Years" by Henry E. Sigerist. Other distinguished contributors and their lectures are as follows: Alan Gregg, "Humanism and Science"; William Healy, "Psychiatry and the Normal Life"; Irwin Edman, "Philosophy as Therapy"; Oscar Riddle, "The Promise of Endocrinology"; and Francis Carter Wood, "What We Do Know About Cancer."

The New York Academy of Medicine is to be congratulated for continuing these lectures and also for making them available in such an attractive printed form.

J. E. S.

Physical Diagnosis By WILLIAM NANCE ANDERSON, B Sc, M D 424 pages, 24 × 15.5 cm Lea and Febiger, Philadelphia 1940 Price, \$4.75

The scope of this book lies midway between the voluminous texts on physical diagnosis and the small handbooks.

The book is divided into three parts. Part I deals with the fundamental principles of physical diagnosis. Proper emphasis is placed upon the importance of a complete history in the systematic study of a case. In this part are discussed the general principles of an examination, inspection, palpation, percussion and auscultation.

Part II deals with the actual method or procedure of a physical examination. Here the proper method for a general complete physical examination is described. Examination of the head, extremities, heart and lungs is stressed. Special systems such as the nervous system are only briefly mentioned.

Part III deals with physical diagnosis in disease. Abnormal physical findings caused by specific cardiac, pulmonary and abdominal diseases are adequately discussed.

The author emphasizes the practical value of mastering the fundamentals of physical diagnosis and points out that the proper interpretation of physical signs and symptoms is the basis for correct diagnosis. He also comments concerning the satisfaction and inspiration derived from the ability to correlate the findings on physical examination with the underlying pathology. The fundamentals of normal and pathological physiology are briefly and clearly discussed with the purpose of explaining the mechanism of production, and interpretation of the various possible findings by physical examination.

Medical students have a tendency to underestimate the need for and importance of performing a careful, thorough physical examination. This attitude has, in a certain measure, been unavoidably aided by the many innovations in all phases of laboratory diagnosis. The author quotes Sir James Mackenzie to illustrate this point: "The seeming exactness of a mechanical device appeals much more strongly to certain minds than a process of reasoning. The sensitive index finger of the experienced doctor can give far more valuable information than all the instrumental methods in the world." Although this statement is not entirely true at the present time, it is still worthy of repetition and should be emphasized in teaching students of medicine.

The fact that there is no bibliography may hamper those readers who wish to refer to the original articles describing various physical findings. A greater number of illustrations would increase the value and understanding of the reading matter. The subject matter is well organized and is simply presented. The style is lucid and promotes easy reading. This book is recommended to the medical student as a brief, practical text on physical diagnosis.

E T L

The A B C of Criminology By ANITA M. MUIR 238 pages, 22.5 × 14 cm Melbourne University Press, Melbourne, Australia 1941

This book "is not intended as a text-book of criminology", the subject matter consists of a series of 13 lectures delivered at the University of Melbourne dealing with practical problems in the field of criminology. The author points out that crime and 'criminal' are relative terms and feels that it is more correct to use such terms as 'offenses against the criminal law' and "offenders against the criminal law". Although the discussion of mental illness is incomplete it should prove of special interest to persons who have neither time nor inclination to read more extensive texts in psychiatry dealing with the various reaction types.

The problem of stealing by children, adolescents, and adults, as well as the discussion of sex crimes is interestingly presented through case studies in which many practical therapeutic suggestions are made. With the exception of the chapter on epi-

lepsy, the remainder of the book is more in keeping with the title. There are two interesting chapters dealing with murder, and the author indicates how many murders might have been prevented by the application of present day technics in mental hygiene and psychiatry. Perhaps the most poignant chapter is the one dealing with the reliability of testimony. The final discussion is concerned with a brief review of modern methods of treatment in the field of criminology, and a chapter on the rôle of mental hygiene in dealing with pre-school children and adolescents.

H W N

Cardiac Classics By FREDERICK A WILLIUS M D Chief, Section of Cardiology, The Mayo Clinic, and THOMAS E KEYS, A B, M A, Reference Librarian, The Mayo Clinic. 858 pages, 25.5 × 18 cm. C V Mosby Co, St Louis, Missouri. 1941. Price, \$10.00.

Dr Willius and Mr Keys have presented us with a delightful volume. Starting with Harvey's "Disquisition on the Motion of the Heart and Blood in Animals," written in 1628 the authors present those works of 52 authors that have come to be considered classics among the studies of the heart and circulation. They are largely reproduced in their entirety and a brief biographical sketch of each author is given.

Most physicians give but little time to the study of the development of knowledge in their profession, perhaps because textual matter is not easy to obtain. This volume renders such an excuse untenable for those interested in the heart and circulation. It also provides fascinating reading.

W S L, JR

COLLEGE NEWS NOTES

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College

Dr Siegfried Block, Brooklyn, N Y
Dr James D Bruce, Ann Arbor, Mich
Dr Ardrey Whidden Downs, Edmonton, Ala
Dr Edward W Hayes, Monrovia, Calif
Dr Frederick E Hudson, Stamford, Tex
Dr H Leon Jameson, Philadelphia, Pa
Dr Henry L Ulrich, Minneapolis, Minn

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members

Books

John W P Love, F A C P, Major (MRC), U S Army—"Outline of Laboratory Course" and "Laboratory Manual"

Reprints

Dr George C Anglin, F A C P, Toronto, Ont—4 reprints,
Dr Irving L Applebaum (Associate), Newark, N J—2 reprints,
Dr J Edward Berk (Associate), Philadelphia, Pa—10 reprints,
Dr Edward G Billings, F A C P, Denver, Colo—1 reprint,
Dr B Earl Clarke, F A C P, Providence, R I—2 reprints,
Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,
John Harper, F A C P, Captain (MC), U S Navy—2 reprints,
Dr Robert F Ives, F A C P, Brooklyn, N Y—1 reprint,
Dr Enrique Koppisch, F A C P, San Juan, P R—1 reprint,
Dr Perry Scott MacNeal (Associate), Philadelphia, Pa—1 reprint,
Dr William E Ogden F A C P, Toronto, Ont—6 reprints,
Dr Richard Kohn Richards (Associate) North Chicago Ill—10 reprints,
Dr Leon Schiff, F A C P, Cincinnati, Ohio—3 reprints,
Dr Sidney Schnur (Associate), Houston, Tex—12 reprints,
Dr Leslie McKnight Smith, F A C P, El Paso, Tex—1 reprint,
Dr William C Voorsanger F A C P, San Francisco, Calif—1 reprint,
Dr William A Winn (Associate), Springville Calif—1 reprint,
Dr Benjamin F Wolverton, F A C P Cedar Rapids Iowa—2 reprints

SPECIAL GIFT TO THE COLLEGE LIBRARY

Dr H Sheridan Baketel F A C P, Jersey City, N J, has made a gift to the College Library of the following medical books, which are not only of great general interest but of additional significance because of their age, all of them having been published about a hundred or more years ago

- ' The First Lines of the Theory and Practice of Surgery, including The Principal Operations"—Samuel Cooper Volumes I and II 4th American Edition, from the 7th London Edition New York, 1844
- " The Principles and Practice of Surgery, Founded on the Most Extensive Hospital and Private Practice, During a Period of Nearly Fifty Years"—Sir Astley Cooper Volume I, 1836 Volume II, 1837 Volume III, 1843 London
- Medical Inquiries and Observations"—Benjamin Rush Volumes I and III 3d Edition Philadelphia, 1809
- " The Study of Medicine"—John Mason Good Volumes I, II, III and IV 5th American Edition, from the last London Edition New York, 1827

FOURTH ANNUAL ROUND-UP OF EASTERN PENNSYLVANIA MEMBERS OF THE COLLEGE

On February 6, 1942, under the direction of Dr Edward L Bortz, College Governor for Eastern Pennsylvania, the Fourth Annual Regional Meeting for this territory was held in Philadelphia with an attendance somewhat in excess of 250 The day's program began with a buffet luncheon at the College Headquarters The following scientific program was given in the afternoon in the Medical Laboratories of the University of Pennsylvania

Recent Studies in Epilepsy "

HAROLD D PALMER, Professor of Psychiatry, Woman's Medical College of Pennsylvania, Associate in Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Pa

" Contact Infection "

JOHN M HIGGINS, Associate in Charge of Pediatrics, Robert Packer Hospital, Sayre, Pa

' Gold Salts and Arthritis "

JOHN LANSBURY, Associate Professor of Medicine, Temple University School of Medicine, Philadelphia, Pa

' Pneumonia Deaths "

KENNETH E QUICKEL, Associate Physician on Indoor Medical Staff and Dispensary Physician in Cardiac Clinic, Harrisburg Hospital, Harrisburg, Pa

" Leukemia "

DANIEL B PIERSON, JR, Assistant Physician, Lankenau Hospital, Philadelphia, Pa

Embohc Occlusion "

DAVID W KRAMLR, Assistant Professor of Medicine, Jefferson Medical College, Philadelphia, Pa

At the adjournment of the scientific session the group assembled for a social hour, followed by a dinner at the Union League Dr William D Stroud Treasurer of the College, was Toastmaster The dinner meeting was addressed by President Roger I Lee, Boston President-Elect, James E Paullin, Atlanta, Secretary General, George Morris Piersol, Philadelphia former President, O H Perry Pepper, Philadelphia Captain A H Allen of the Philadelphia Navy Yard, and Captain Henry L Dollard, Commanding Officer of the Philadelphia Naval Hospital Among special guests were Dr Roy R Snowden, College Governor for Western Pennsylvania, Dr Lewis B Flinn College Governor for Delaware, Dr Louis Krause, College Governor for Maryland, Dr George H Lathrope, College Governor for New Jersey Dr Wallace M Yater, College Governor for the District of Columbia Dr William Pearson, Dean of Hahnemann Medical College, Dr William Pepper, Dean of the University of Pennsylvania School of Medicine Dr William H Perkins, Dean of Jefferson Medical College, and Dr George H Meeker Dean Emeritus of the University of Penn-

sylvania Graduate School of Medicine. A quartet from the Philadelphia Orpheus Club provided music and songs, and Mr Henry W Doughton provided stories. Many Fellows and Associates of the College were present from New Jersey and Delaware.

These regional meetings are of significant value in that they bring the local members closer together, expand general good Fellowship and provide an opportunity to keep the members informed of the activities of the College in a more intimate fashion.

Dr Lea A Riely, F A C P, Oklahoma City, College Governor for Oklahoma, reports that the Oklahoma City Internists held a Washington's Birthday Clinic at the University Hospitals, Oklahoma City, on February 23, 1942, with the following program, and with 77 physicians registered, 45 of whom were from outside of Oklahoma City. Under similar auspices these clinics have been held in Tulsa, Chickasha and Ada, Oklahoma.

Allergy Clinic

Dr P M McNeill, F A C P, Oklahoma City

Diabetes Clinic

Dr Bert F Keltz, F A C P, Oklahoma City

Cardiac Clinic

Dr W W Rucks, Jr, F A C P, Oklahoma City

Clinical Pathological Conference

Dr Hugh Jeter, F A C P, Oklahoma City

Luncheon Forum

Conducted by Dr A W White, F A C P, Dr L J Moorman, F A C P, Dr George A LaMotte, Dr Lea A Riely, F A C P, all of Oklahoma City

Chest Clinic

Dr Floyd Moorman (Associate, A C P)

Clinic on Anemias

Dr Wann Langston, F A C P Oklahoma City

Arthritis Clinic

Dr William K Ishmael, Oklahoma City

Dr Andrew C Woofet, F A C P Parkersburg W. Va., has been elected President of the Parkersburg Academy of Medicine.

Dr Harry Mandelbaum, F A C P, Brooklyn, N. Y., has been appointed Attending in Medicine at the Jewish Sanitarium for Chronic Diseases.

Dr Julius H Comroe, F A C P, York, Pa., is the internist in the Cardiovascular Division of the Army Medical Examination Center "D," at the Harrisburg, Pa., Military Post. He has been serving also as the internist for the Pennsylvania State Medical Advisory Board No. 4, which comprises nine counties.

Dr William H Watters, F A C P, has been appointed to the department of Legal Medicine in Harvard Medical School. Prior to this appointment, he resigned an appointment as one of the Medical Examiners of Suffolk County (Boston) and had previously resigned as Professor of Preventive Medicine in Boston University School of Medicine. The new appointment will consist largely of summer postgraduate activities and will enable him to devote more attention to his winter practice in Miami.

Associated with him in Miami is his son, Dr Preston H Watters, F A C P, who during the summer is Instructor in Medicine at the University of Rochester and a Visiting Physician at the Strong Memorial Hospital.

The 38th Annual Congress on Medical Education and Licensure was held in Chicago Ill, February 16-17, 1942. Among the speakers were

Dr Jonathan C Meakins, F A C P, Montreal, Que—"The Effect of the War on Medical Education in Canada",

Ross T McIntire, F A C P, Rear Admiral (MC), U S Navy, The Surgeon General—"Medical Education from the Standpoint of the Navy Medical Corps",

George F Lull F A C P, Colonel (MC), U S Army—"Current Medical Personnel Problems of the Army",

Dr Thomas Parran, F A C P, The Surgeon General, U S Public Health Service—"Needs of the Public Health Service for Medical Personnel in National Defense Activities",

Dr Walter E Vest, F A C P, Huntington, W Va—"Citizenship as Related to Licensure"

James C Magee, F A C P, Major General (MC), U S Army, The Surgeon General, has ordered the members of the Northwestern University's General Hospital Unit No 12 to active duty at Camp Custer, Mich. The Northwestern Unit is the first of the three hospital units organized in Chicago to be called to active duty. Among the College members who were called to duty with this unit were

M Herbert Barker, F A C P, Lieutenant Colonel (MRC), U S Army,

Richard B Capps (Associate), Major (MRC), U S Army,

Eugene L Walsh (Associate), Major (MRC), U S Army,

Richard H Young, F A C P, Major (MRC), U S Army

The 4th Annual Forum on Allergy was held in Detroit, Mich, January 10-11, 1942. This meeting consisted of a series of study groups, symposia, lectures and educational exhibits. Among the leaders of the study groups were

Dr Karl D Figley, F A C P, Toledo, Ohio—"Perennial Allergic Coryza",

Dr Herbert J Rinkel, F A C P, Kansas City, Mo—"Food Allergy",

Dr J Warrick Thomas, F A C P, Cleveland, Ohio—"Ocular Allergy",

Dr Orval R Withers (Associate), Kansas City, Mo—"Gastro-intestinal Allergy, Cyclic Vomiting and Beginning Migraine",

Dr Frank R Menagh, F A C P, Detroit, Mich—"Neurodermatitis in Adults",

Dr Milton B Cohen, F A C P, Cleveland, Ohio—"Physical Stigmata of Allergy",

Dr Ralph Bowen, F A C P, Houston, Tex—"Asthma in Children",

Dr Theodore L Squier, F A C P, Milwaukee, Wis—"Food Allergy",

Dr Homer E Prince, F A C P, Houston, Tex—"Mold and Smut Allergy",

Dr Samuel M Feinberg, F A C P, Chicago, Ill—"Asthma in Adults over 45 Years of Age",

Dr Leon Unger, F A C P, Chicago, Ill—"Allergic Conjunctivitis",

Dr John Sheldon (Associate), Ann Arbor, Mich—"Allergic Conjunctivitis"

At the Symposium on Food Allergy, Dr Clark P Pritchett (Associate), Columbus, Ohio, discussed "The Dietary Management," and at the Symposium on Hay Fever Dr McKinley London (Associate), Cleveland, Ohio, discussed "Pollen and Pollen Extract in Oil"

At the Annual Forum Luncheon, January 11, Dr Milton B Cohen, F A C P, Cleveland, Ohio, presented the Forum Gold Medal to Dr William W Duke, F A C P, Kansas City, Mo. Later in the afternoon Dr Duke delivered the Annual Forum Lecture. His subject was "The Beginning of Clinical Allergy in the United States"

Dr Harry L Alexander, F A C P, St Louis, Mo, delivered a special lecture to the Forum entitled "The Broader Aspects of Allergy"

The following Educational Exhibits were presented by members of the College

"Demonstration of Twenty Roentgenograms of the Chest in Cases First Thought to Be Asthma but Which Proved to Be Something Else"—Dr George L Waldbott, F A C P, Detroit, Mich ,

"Insects Which Act as Antigens Caddis and May Flies"—Dr Karl D Figley, F A C P, Toledo, Ohio,

"Insects Which Act as Antigens Daphnia"—Dr Karl D Way (Associate), Akron, Ohio,

"The Story of the Asthmatic Child"—Dr Ralph Bowen, F A C P, Houston, Tex ,

"The History of Asthma"—Dr Leon Ungei, F A C P, Chicago, Ill

"Ocular Allergies"—Dr J Warrick Thomas, F A C P, Cleveland, Ohio

On January 9, Pre-Forum Clinics on Allergy were conducted at the University Hospital in Ann Arbor, Mich Among those who presented clinics were

Dr Herman H Riecker, F A C P, Associate Professor of Internal Medicine—"Bronchiectasis, Allergic Factors",

Dr Udo J Wile, F A C P, Professor of Dermatology and Syphilology and Chairman of the Department of Dermatology and Syphilology—"Drug Eruptions",

Dr Cyrus C Sturgis, F A C P, Professor of Internal Medicine, Director of Simpson Memorial Institute, and Chairman of Department of Internal Medicine—"Hemorrhagic Diathesis",

Dr John M Sheldon (Associate), Assistant Professor of Internal Medicine—"Preparation of Fungus Extracts"

Dr Hugh J Morgan, F A C P, Nashville, Tenn, a Colonel in the Medical Reserve Corps of the U S Army, has been called to active duty Dr Morgan will serve as Head of the Subdivision of Medicine, Professional Services Division, in the office of the Surgeon General, Washington, D C

The 57th Annual Session of the Mid-South Post Graduate Medical Assembly was held in Memphis, Tenn, February 10-13, 1942 Among the speakers were

Dr Francis M Rackemann, F A C P, Boston, Mass—"The Causes of Asthma, Their Diagnosis and Treatment",

Dr Irvine H Page (Associate), Indianapolis, Ind—"The Nature and Treatment of Arterial Hypertension",

Dr David C Wilson, F A C P, Charlottesville, Va—"Practical Methods of Diagnosis in Nervous and Mental Diseases",

Dr Frank N Wilson, F A C P, Ann Arbor, Mich—"Angina Pectoris",

Dr Burrill B Crohn, F A C P, New York, N Y—"The Chronic Diarrheas",

Dr Clifford J Barborka, F A C P, Chicago, Ill—"Medical Management of Gall-bladder Diseases"

At the recent annual meeting of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc, in Washington, D C, Joseph F Siler, F A C P, Colonel (MC), U S Army, Retired, was elected President, and Merritte W Ireland, F A C P, Major General (MC), U S Army, Retired, was elected Secretary

Dr Burrill O Raulston, F A C P, Los Angeles, spoke on "Newer Sulfonamides," and Dr Howard F West, F A C P, Los Angeles, spoke on "Diabetics Today" at a

meeting of the Western section of the American Laryngological, Rhinological and Otolological Society at Los Angeles, Calif, February 1, 1942

Dr Peter T Bohan, F A C P, Kansas City, Mo, spoke on "Casual Factors in Angina Pectoris and Coronary Infection" at a recent meeting of the Pratt County (Kan) Medical Society

Dr Felix J Underwood, F A C P, Jackson, Miss, was one of the speakers at the recent annual meeting of the Louisiana Public Health Association in New Orleans

Charles F Craig, F A C P, Colonel (MC), U. S Army, Retired, has been appointed a member of the Editorial Board of the Journal of the National Malaria Society, which is a new annual periodical

Dr William C Menninger, F A C P, Topeka, spoke on "The Psychiatrist in Relation to the Examining Boards" at a recent meeting of the Missouri-Kansas Neuropsychiatric Association held in Topeka, Kan Dr Alexander R MacLean, F A C P, Rochester, Minn, spoke on "Postural Psychoneuroses" at the banquet of this meeting.

Dr Frank R Menne, F A C P, Portland, Ore, was the guest speaker at the recent annual meeting of the Seattle Surgical Society Dr Menne spoke on "Lymphosarcoma of Small Intestine with Report of Two Cases Receiving Surgical Intervention"

Dr Anton J Carlson, F A C P, Chicago, Ill, delivered the first annual A C Helmholtz Lecture, January 16, 1942, under the auspices of the University of Wisconsin Medical Society at Madison The subject of Dr Carlson's address was "Some Unknown Problems in the Physiological Pathology of Aging"

Dr Harold M Coon, F A C P, Madison, has been elected a member of the Board of Directors of the Wisconsin Hospital Association

Dr Seale Harris, F A C P, Birmingham, Ala, spoke on "The Food Factor in Winning the War" at a meeting of the Northwestern Division of the Medical Association of the State of Alabama in Florence, January 28, 1942

Among the guest speakers at the 10th Annual Midwinter Post Graduate Clinics of the Colorado State Medical Society held in Denver, February 19-21, 1942, were

Dr John A Toomey, F A C P, Cleveland, Ohio—"Chemotherapy in Infectious Diseases",

Dr Benjamin H Orndoff, F A C P, Chicago, Ill—"Endometriosis Its Relation to Sterility and Other Conditions of the Female Pelvis",

Dr Edward H Hashinger, F A C P, Kansas City, Mo—"Hypothyroidism"

Dr Marine R Warden, F A C P, Danville, Ill, spoke on "Radiology" at a recent meeting of the Fountain-Warren County (Ind) Medical Society at Kramet

Dr Alexander B Gutman, F A C P, New York, N Y, spoke on "Biochemical Aids to Roentgenologic Problems in the Differential Diagnosis of Bone Disease," and

Dr Cornelius P Rhoads, F A C P , New York, N Y , spoke on "Recent Studies in the Production of Cancer by Chemical Compounds" at the Eastern Conference of Radiologists held in New York City, January 23-24, 1942

In order to acquaint the public with the best methods for the prevention of disease and promotion of health, the Town Club, of Oklahoma City, Okla , with the approval of the Oklahoma County Medical Association, presented a series of free health talks The program included

January 7—"Colds, Influenza and Pneumonia," Dr Floyd Moorman (Associate),
 February 4—"Heart Disease Its Prevention and Care," Dr Bert E Mulvey, F A C P ,
 March 4—"The Brain in Health and Disease," Dr C J Fishman, F A C P .
 April 1—"Your Weight and How to Control It," Dr Bert F Keltz, F A C P

Dr Cecil J Watson, F A C P , Minneapolis, Minn , was one of the guest speakers at a postgraduate course in Therapeutics conducted by the University of Manitoba Faculty of Medicine in Winnipeg, February 11-13, 1942 Dr Watson spoke on "Some Physiological and Clinical Aspects of Jaundice"

Dr Joseph H Barach, F A C P , Pittsburgh, Pa , addressed the Indiana County Medical Society, at Indiana, Pa , on February 12, 1942 His subject was "The Treatment of the Complications of Diabetes"

The Hermann M Biggs Memorial Lecture which is held annually in Hosack Hall at The New York Academy of Medicine under the auspices of the Committee on Public Health Relations will be delivered this year on Thursday, April 2nd, at 8 30 p m , by Dr James S McLester, F A C P , Professor of Medicine at the University of Alabama, Chairman of the Council on Foods and Nutrition of the American Medical Association, and Chairman of the Subcommittee on Medical Nutrition of the National Research Council The subject of the lecture will be "Nutrition and the Nation at War"

Dr Jose Bisbe, F A C P , General Secretary of the Medical Federation of Cuba, Havana, reports that that organization has organized a Committee on Medical Preparedness in connection with the war, under the direction of Dr Pedro Fariñas This Committee is integrated by delegates from all important medical societies of Cuba and with organizations closely related to the medical profession, such as those representing nurses, pharmacists, women's social clubs, the Reporters Association, etc

The following sub-committees have been set up to accomplish the objectives of this Committee

- Sub-committee on Foods and Nutrition
- Sub-committee on Medical First Aid
- Sub-committee on Pharmacy
- Sub-committee on Preventive Medicine and Public Health
- Sub-committee on Technical Training
- Sub-committee on Medical Mobilization

A series of conferences has been initiated, the first one having taken place at the Academy of Sciences on January 23, with a remarkable attendance Dr Moises Cuedrak and Dr Guillermo Garcia Lopez made the presentations on "National Organization of Blood Transfusion Services" and "Importance of the Official Measures Adopted to Guarantee a Correct Diet for the Population in All Possible Emergencies," respectively

The Cuban Committee on Medical Preparedness is undertaking a complete re-organization of their records, questionnaires have been sent out to the four thousand physicians belonging to the Federation to have the physicians properly classified, and a study is being made of those measures which will insure an adequate diet and a proper stock of medicines. Courses are being organized for the technical training of young physicians, nurses and women and special attention is being given to measures for preventive medicine.

Dr. Bisbe, as General Secretary of the Medical Federation of Cuba expresses the earnest desire and firm determination of the doctors of Cuba to cooperate with the medical profession of the United States in this emergency to the total extent of their ability.

REDUCTION IN DUES TO MEMBERS ON ACTIVE MILITARY SERVICE

The American College of Physicians has gone on record, through its Board of Regents, to help and to alleviate the burden of dues of members called to active military service. Regulations have been established whereby the dues of all Associates and Fellows entering upon military service are automatically reduced to \$10.00, this amount to entitle the members to fully active and participating membership as before. Furthermore, if the reduced dues should be a burden a member may apply by letter to the Committee on Public Relations of the College stating the situation, and the Board of Regents may authorize further reduction or the full remission of dues.

The primary necessity at present is the winning of the War. A secondary, but nevertheless important, object should be to preserve our American Institutions. Comparable organizations on the European Continent lie buried with their martyrs. Our American Institutions must have some support to carry on during this War. It is merely asked that those members who can afford to do so shall continue paying some dues. The College, after all, has been doing a great deal for the War effort, and will do more so far as its means provide. For more than a year, the College has foreseen the present needs and was chiefly responsible, financially and by administration, for setting up an office for the classification of 28,000 physicians, including internists, pediatricians, medical Reserve Officers and general practitioners, with respect to their qualifications and availability for military service. This work is still going on, and there are more than 35,000 additional physicians to be evaluated. This work has been carried on in the office of our President-Elect, Dr. James E. Paullin, of Atlanta. One of the objectives of this work has been to see that physicians are used according to their qualifications and experience—to have an internist doing Internal Medicine, not Surgery and vice versa. The College, during February, organized and presented a series of Postgraduate Lectures for the Medical Officers in a large Naval Hospital and are expecting to extend this program to other large military hospitals, thus affording an opportunity for the Medical Officers to obtain advance training, which, in War times, is often not available to them otherwise. Still another contribution that was made more than a year ago was an appropriation of \$10,000.00 for a rather complicated military research problem in connection with blood plasma, the work being carried out by Professor Cohn, of Harvard. This appropriation was made through the National Research Council, Committee on Medicine, at a time when no funds were being made available by the Federal Government. Although the project itself has been of great value, action by the College in making this appropriation has more significance from the standpoint that it had prime importance in bringing forth adequate appropriations from the Government for such projects in the present and future.

Many members of the College are making real contributions to the War effort by directing numerous and important committees in the National Research Council and other bodies in Washington. The College is justifying itself in civilian practice in postgraduate education and in many other directions. It fully merits the continued support of all members who can afford to make some contribution in dues. Those in

a more favorable position may feel a patriotic obligation not only toward the College but toward other American Institutions to increase their zeal and their loyalty, and to make their contributions in dues to help make up for those on active military service who must, of necessity, in some instances, be carried free

CONSERVATION OF SCHOLARLY JOURNALS

The American Library Association created this last year the Committee on Aid to Libraries in War Areas, headed by John R. Russell, the Librarian of the University of Rochester. The Committee is faced with numerous serious problems and hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

One of the most difficult tasks in library reconstruction after the first World War was that of completing foreign institutional sets of American scholarly, scientific, and technical periodicals. The attempt to avoid a duplication of that situation is now the concern of the Committee.

Many sets of journals will be broken by the financial inability of the institutions to renew subscriptions. As far as possible they will be completed from a stock of periodicals being purchased by the Committee. Many more will have been broken through mail difficulties and loss of shipments, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the Committee already give evidence that it will be enormous.

With an imminent paper shortage attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the Committee hopes to enlist the cooperation of subscribers to this journal in preventing the sacrifice of this type of material to the pulp demand. It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

Questions concerning the project or concerning the value of particular periodicals to the project should be directed to Wayne M. Hartwell, Executive Assistant to the Committee on Aid to Libraries in War Areas, Rush Rhees Library, University of Rochester, Rochester, New York.

AMERICAN PSYCHIATRIC ASSOCIATION OPENS CONTEST FOR EMBLEM DESIGN

Dr. J. K. Hall, F.A.C.P., Richmond, Va., President of the American Psychiatric Association has announced a contest for the design of an emblem for that society. The emblem will be used in the centennial celebration in 1944 of the American Psychiatric Association which is the oldest organization of medical specialists in the country.

Artists, art teachers and students are invited to compete. Prizes amounting to a total of \$500 will be awarded. Three prizes of \$100 each will be awarded for the three best drawings, selected by a jury which includes an architect, a painter and a sculptor. From these three drawings, the Council of the Association will select the one which they consider most suitable for their purpose. This drawing will receive an additional award of \$200 and will become the property of the Association. All remaining drawings will be returned.

The design may be executed in any medium. It should be rectangular and preferably vertical. To facilitate handling the size of the mat should be 11 by 14 inches. Artists are requested not to place their signatures on the face of the drawing or in a place which is concealed under the mat. The full name and address of the contestant should appear on the reverse side.

Drawings should be sent to the American Psychiatric Association, 9 Rockefeller Plaza, New York City, and should reach that office not later than April 15, 1942.

Inquiries concerning the general ideas of the contest, or details of the history or activities of the American Psychiatric Association, which might be helpful to the artist, are to be addressed to the Chairman of the Committee on History of Psychiatry Dr Gregory Zilboorg, 14 East 75th Street, New York City

The artist is free to use any ideas he deems suitable. However, in order that the design should represent the aims of the American Psychiatric Association, its purpose in the study of mental diseases, and its social and cultural importance, it is suggested that the artist write to Dr Zilboorg for the explanatory folder containing this information

ERRATA

On page 182 of the January, 1942, issue of this journal appeared a report on the Regional Meeting of the Illinois members of this College at Chicago on December 6, 1941. Dr Fred Drennan took the place of Dr Ralph C Brown as one of the clinicians in the Clinico-pathologic Conference

POSTGRADUATE COURSE No 9, GASTRO-INTESTINAL DISEASES, WITHDRAWN

It was with regret and disappointment on the part of the Director and of the College that Postgraduate Course No 9, Gastro-intestinal Diseases, at the University of Chicago, April 6-18, 1942, under Dr Walter L Palmer, had to be withdrawn on March 10. The war situation with greater pressure than usual at the institution, with a greater undergraduate teaching load, coupled with the fact that the registration for this course was comparatively small, is responsible for the action taken. Dr Palmer expresses the hope that when the war emergency has passed, he and his associates will again have the opportunity to cooperate with the College in its postgraduate program

OBITUARIES

DR SAMUEL WALDRON LAMBERT, SR

Dr Samuel Waldron Lambert, Sr., was born in New York City, June 18, 1859, and died at his home, 101 East 72 Street, New York City, on Monday, February 9, 1942, at the age of eighty-two years. He was the son of Dr Edward W Lambert and the former Martha Waldron. His father was a prominent New York physician and his brothers, the late Dr Alexander Lambert, personal physician and intimate friend of President Theodore Roosevelt, and Dr Adrian V S Lambert, surgeon of New York City.

Dr Lambert was a Trustee and former President of the New York Academy of Medicine. He received his A B degree from Yale University in 1880 and Ph B from Yale University in 1882, M D from the College of Physicians and Surgeons in 1885. After the completion of his Internship at Bellevue Hospital, he attended clinics in Berlin, Munich, and Vienna for two years. On his return to New York in 1889, Dr Lambert began the practice of medicine and obstetrics and in the next year he introduced bedside teaching of medical students at the Midwifery Dispensary founded by himself and Dr James Markoe. His influence in the organization of hospital services and particularly their integration with the teaching activities of the medical schools in this City grew progressively. In its first year the

newly formed Dispensary trained more than two hundred students and in 1892, because of its success, it was amalgamated with the Society of the Lying-in Hospital

Dr Lambert served as Attending Physician to Nursery and Childs Hospital, 1890-1898, Midwifery Dispensary, 1890-1893, New York Lying-in Hospital, 1892-1903, New York Hospital, 1896-1909, and St Luke's Hospital, 1906-1929. He was Professor of Applied Therapeutics, 1903-1919, Columbia University College of Physicians and Surgeons, Professor of Clinical Medicine, 1904-1929, Columbia University College of Physicians and Surgeons, and Dean of Columbia University College of Physicians and Surgeons from 1904-1919.

Dr Lambert was Consulting Physician to the Ruptured and Crippled Hospital, French Hospital, Bronx Hospital, St Luke's Hospital, Fifth Avenue Hospital, New York Orthopedic Hospital, Presbyterian Hospital, Reconstruction Hospital, Neurological Institute, St Vincent's Hospital, Home for Incurables, Colored Orphan Asylum, White Plains Hospital, Southside Hospital, Laurence Hospital, St John's Riverside Hospital and Tarrytown Hospital. He was also a Trustee of the Roosevelt Hospital from 1904-1919.

Years ago Dr Lambert proposed the creation of a medical center in this City, a proposal which was enthusiastically received. He prepared a program for the establishment of such a center in 1915 and saw its realization thirteen years later in the building of the Medical Center. He was also a leader in the fight for city cleanliness and the long struggle against the Volstead Act's limitations on the prescription of liquor for medicinal purposes. Dr Lambert, at the time he was President of the New York Academy of Medicine, was leader in the formation of the Committee of Twenty on Street and Outdoor Cleanliness, and was a supporter of moderate drinking as an aid to good health, a subject on which he gave many dissertations, he was a vigorous opponent of prohibition and particularly fought the Congressional limitation on physician's rights to prescribe liquor to patients. Under the Volstead Act physicians could not prescribe more than one pint of liquor to a patient every ten days, which Dr Lambert called "a legislative lie." He fought this law from 1922 until the Celler-Copeland bill ended it in March 1933. He brought a test case against it which went to the Supreme Court, where he lost the fight by a five to four decision but he continued to urge a national organization of physicians to fight the Eighteenth Amendment and the Volstead Act. In carrying the test case through the courts, he acted as President of the Association for the Preservation of Constitutional Rights.

As Dean of Columbia University College of Physicians and Surgeons, during the World War, Dr. Lambert devoted his efforts and those of the Medical College to turning out the greatest possible number of physicians for service with the American Forces. At the suggestion of and in cooperation with the Government the College graduated the class of 1919 two years ahead of time, giving the Government the services of more than one hundred additional physicians.

Dr Lambert engaged in non-medical, as well as medical writings, was a book collector and developed a large library, a considerable portion of which was devoted to angling literature, especially Waltoniana and Cottoniana. His writings included a volume written with Dr George M Goodwin entitled "Medical Leaders," a criticism of Dickens, "When Mr Pickwick went Fishing," and many shorter articles published in the Bulletin of the New York Academy of Medicine and in various issues of "The Proceedings of the Charaka Club." He also contributed twenty-seven medical papers.

Dr Lambert received an honorary M A from Yale University in 1905 besides one from Columbia University. He was a member of the following medical societies: the Charaka Club, the Clinical Society of New York, Practitioners Society of New York, Alumni of Bellevue Hospital Society, Medical and Surgical Society of New York, Association of American Physicians and the American Gastro-Enterological Society. He was an original member of the Interurban Clinical Club, founded by Sir William Osler in 1905, which was devoted to advances in medical teaching and research. He was also a member of the Association of American Medical Editors and Authors, the New York Academy of Medicine, New York County Medical Society, New York State Medical Society, Fellow of the American Medical Association, and Fellow of the American College of Physicians since 1931.

Among his clubs were the Century Association, Grolier Club, Union Club, Racquet and Tennis Club, University, Yale, Graduates Club of New Haven, South Side Sportman's, Oquossoc Angling Association of Maine, Megantic Fish and Game Corporation and Psi Upsilon, Nu Sigma Nu, and Alpha Omega Alpha fraternities.

Dr Lambert married Elizabeth Willets on October 21, 1893, who survives him. Also surviving, besides his brother, Dr Adrian V S Lambert, are a son, Dr Samuel W Lambert, Jr, two daughters, Mrs Gillet Lefferts and Mrs J Ogden Bulkley.

CHARLES F TENNEY, M D, F A C P
Governor for Eastern New York

DR GEORGE WASHINGTON HALL

On October 25, 1941, medicine lost a grand gentleman and a great physician in the person of George Washington Hall. Dr Hall was born in Crawfordsville, Indiana, in 1869, graduated from Wabash College in 1890, and from Rush Medical College in 1893. He received both his B A and M A degrees while at Wabash. At the age of 24 he was on his way to various European clinics to increase his knowledge.

After graduation in medicine, Dr Hall became an associate of Dr Daniel Brower who was, at that time, Professor of Materia Medica at Rush. In the same office with Dr Brower was Dr E Fletcher Ingals, Professor of Diseases of the Chest and of the Nose and Throat. It was, therefore, quite natural for Dr Hall to become primarily an internist.

In 1902, he was an instructor in the Department of Medicine and in 1907 assistant professor.

Dr Brower gradually turned his attention to the field of neuropsychiatry in which he became eminent Dr Hall followed this change and from 1911 advanced step by step until he became professor of nervous and mental diseases at Rush

He was attending neurologist on the staff of Cook County Hospital from 1907 until 1918, later transferring to the Psychiatric service In 1916, he was appointed senior neurologist at St Luke's hospital which position he continued to hold until his death In 1932 he was president of the medical staff of St Luke's Hospital

During his sojourn in Europe, he studied at the National Hospital, Queens Square in London and attended clinics in Berlin, Vienna and Munich He was a member of the American Neurological Association, the Neurological Society of Chicago, past president of the Central Neuro-Psychiatric Association, and member of the Board of Governors of the Institute of Medicine of Chicago He had been a Fellow of the American College of Physicians since 1930

During later years, his life was interrupted by repeated attacks of coronary occlusion In spite of the advice of his family, friends, physicians and others, he continued in the active pursuit of a busy practice and literally died with his boots on while attending a meeting of the Central Neuro-Psychiatric Association

Dr Hall was primarily a physician who had become an excellent neurologist and neuro-psychiatrist His early training made him very appreciative of the close relationship of general disease to nervous and mental change His students, interns, residents and associates recognized in him a fine doctor whose knowledge was beyond the strict limitations of his own field He was wont to check the patient's general condition, his blood pressure, pick up an auricular fibrillation as a basis for a cerebral attack, call the turn on a questionable syphilitic, recognize the association of the less obvious blood dyscrasias, lung abscess or general infection to the nervous and mental changes which might be at the moment outstanding

He made much of his hunches His uncanny arrival at a correct diagnosis on clinical grounds at times belied the value of numerous laboratory procedures He was pushed by competition with excellent men both within his own hospital group and without He was at all times respected and admired by these men

Dr Hall was an inspiration to many a young man A pat on the back, an invitation to golf, to bridge, to poker carried with it the unspoken suggestion—"it is my duty and my pleasure to help him along a bit "

He enjoyed life to the fullest, had a host of friends, young and old, enjoyed their companionship, was respected and admired by them and will be remembered with the affection that comes from recognition and admiration of an understanding that was more human than usually touches those who reach high peaks

Dr Hall was a grand sportsman. He was not only an ardent golfer but a good one and in his heyday could putt like a wizzard, drive straight but not long, approach close to the pin and make tough going for even the best. He received much pleasure from his golf and the associates of his golfing days. As he facetiously remarked more than once, he was known as a golfer among the neurologists and as a neurologist among the golfers.

He played a fine hand at bridge or poker and after the tournaments sought out a corner and turned in a pretty demonstration of his "extramural" activities.

There was always a good story on tap for his rounds at St. Luke's, at the tournaments in the evening, at the medical societies, at banquets, at his various clubs or within the privacy of his own home.

There is nothing unkind that one can say of George Hall. His death will be a real loss to Chicago medicine and to medicine in general. Others will come but not excel this fine gentleman of good humor,—kindly, thoughtful, gentle, honest and stimulating. He has gone to his rest covered with happy remembrances of his urge to help others and the satisfaction that comes from a duty well performed.

His burial service was so simple, so honest and so personal that it would have made George Hall very happy. From his throne above, he surely can look down and say, "It was a grand old earth, I was always happy and they liked me."

GEORGE H. COLEMAN, M.D., F.A.C.P.

DR. CHARLES HATCH STODDARD

Dr. Charles Hatch Stoddard, F.A.C.P., was born in East Troy, Wisconsin, 1869. Following premedical work for three years at the University of Wisconsin he was graduated from the University of Illinois College of Medicine in 1892. During the next two years he was occupied with post-graduate study in Vienna and Strassburg. Participation in medical responsibilities in his community included the following. He was the first Medical Director and Superintendent of the Bluemound Sanatorium in 1907, a member of the first Wisconsin Committee of the International Congress on Tuberculosis, 1908, for many years he was a member of the staff at such hospitals as Columbia, Mount Sinai, St. Mary's, Milwaukee County and the Milwaukee Hospital. He served the Wisconsin Anti-Tuberculosis Association as a member of the Board of Directors, later as Vice-president for nineteen years, and as President in 1931 and 1932, following which he was Recording Secretary from 1933 to his death. Twice he was Vice-president of the Milwaukee Academy of Medicine, he was President in 1927 of the Milwaukee County Medical Society. In 1916 he was a member of the House of Delegates of the American Medical Association. He was made a Fellow of the American College of Physicians in 1926. During the first World War he served as a Major in the Medical Corps in the Wisconsin National Guard. Death came December 17, 1941, of chronic nephritis.

Those whose acquaintance with Dr Stoddard dates back many years recall the geniality of his early days in the profession. He established himself in Milwaukee in the early nineties. Several decades before this, his father, also a physician, erroneously concluding that the trend of commercial life led to the interior of the State, settled in practice in a small community, then finally established himself in LaCrosse, where his son spent his earliest years. It was perhaps natural for him to remain in the State of his birth and to cast his lot in its metropolis—now far outgrown his pioneer father's anticipation.

Although in the early years of his professional life Dr Stoddard's health was undermined and necessitated a break in practice, he was able to resume work, and continued unremittingly up to a year or two before his death. With the knowledge that he had an illness that spelled his doom, no word of complaint was uttered, his stoicism was uncanny and almost unreal to those associated with him, his family was not to know the agony that was his.

Dr Stoddard's fine, upright character, his broad educational background, his inherent refinement of manner and action all served to single him out as one endowed by nature with the qualities that must make and adorn the successful physician. He instilled confidence, his integrity won the attachment of friend and patient, he was dignified but not unbending, his unassuming attitude toward his confreres won their respect.

No one can gain a respected position in a community without having earned this regard. And surely it may be said of Dr Stoddard that the many who treasure his memory do so from a sense of honest appreciation of the man's genuine worth.

ARTHUR J. PATEK, M.D., F.A.C.P.

DR CHARLES CLAGETT MARBURY

Dr Charles C. Marbury, F.A.C.P., Washington, D. C., died December 10, 1941, of coronary thrombosis, aged 71.

Dr Marbury was born at Upper Marlboro, Maryland, July 11, 1870. He attended the Charlotte Hall Academy, received his B.A. degree from Saint John's College, Annapolis, in 1890, and graduated in medicine from Georgetown University School of Medicine in 1893. From 1903 to 1925 he was Professor of Clinical Medicine at his Alma Mater, and from 1925 to the time of his death, Professor of Clinical Medicine Emeritus. He was a veteran of the Spanish-American and World wars; since 1928, member of the Consulting Staff of the Central Dispensary and Emergency Hospital, member of the Board of Visitors and Governors of Saint John's College, 1924 to 1938, former President of the Clinical Society of the District of Columbia and of the Clinico-Pathological Society, member of the Medical Society of the District of Columbia, Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1928.

Dr Marbury was a quiet man, of pleasing personality and was well liked.

MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA

DECEMBER 14, 1941

The regular autumn meeting of the Board of Regents was held at the College Headquarters, December 14, 1941, starting at 10 15 a m President Roger I Lee presided, and the following were in attendance

Roger I Lee	<i>President</i>
James E Paullin	<i>President-Elect</i>
D Sclater Lewis	<i>First Vice-President</i>
Samuel E Munson	<i>Thud Vice-President</i>
William D Stroud	<i>Treasurer</i>
George Morris Piersol	<i>Secretary-General</i>
Francis C Blake	
Reginald Fitz	
Charles T Stone	
J Morrison Hutcheson	
Walter W Palmer	
O H Perry Pepper	
James D Bruce	
T Homer Coffen	
Ernest E Irons	
Jonathan C Meakins	
Hugh J Morgan	
Maurice C Pincoffs	
Charles H Cocke	
John A Lepak	<i>General Chairman, Twenty-sixth Annual Session</i>
Warren Thompson	<i>Member, Committee on Nominations</i>
Edward L Bortz	<i>Chairman, Advisory Committee on Postgraduate Courses</i>

Mr E R Loveland, Executive Secretary, acted as Secretary

The Secretary, Mr Loveland, read abstracted Minutes of the meetings of the Board held at Boston during April, 1941 These were approved with a correction by Dr Paullin of "financial support of the National Research Council"

The Secretary read communications of regret from Drs William J Kerr, Egerton L Crispin, Gerald B Webb, David P Barr and Thomas T Holt, members who were unable to be in attendance

Other communications included

- (1) Report that President Lee had appointed Dr Wallace M Yater, Governor for the District of Columbia, as official College representative at the installation of the new President of the American University, October 19, 1941,
- (2) A letter from Dr Hugh S Cumming, President of the Gorgas Memorial Institute, notifying the College that the By-Laws of the Institute provided "that the President of the American College of Physicians shall be a member ex officio of that Institute",

(President Lee had been unable to attend the meeting in November, due to the notice not reaching him in time)

- (3) A report that Dr Francis G Blake had been appointed by President Lee, October 25, 1941, to succeed Dr James H Means, resigned, as one of the College representatives on the Advisory Council on Medical Education ,
 - (4) A digest of letters received from Dr Cecil M Jack, Governor for Southern Illinois, F G Norbury, of Jacksonville, and Third Vice President Samuel E Munson, of Springfield, concerning division of the Governors' territories in Illinois
- (No action was taken because Dr LeRoy H Sloan, Governor for Northern Illinois, had not yet filed his report, map and suggestions Therefore, this item shall be placed on the agenda for the next Regents' meeting)

Dr George Morris Piersol, as Secretary-General, reported as follows

- (1) The deaths of 32 Fellows and 3 Associates since last meeting of this Board

Fellows

Albee, George M	Worcester, Mass	August 10, 1941
Alvarez, John Arthur	Houston, Tex	October 19, 1941
Baird, Raleigh William	Dallas, Tex	July 13, 1941
Bishop, Louis Faugeres, Sr	New York, N Y	October 6, 1941
Burns, Gerald Ross	Halifax, N S, Can	November 16, 1941
Campbell, Edward Everett	Columbus, Ohio	July 4, 1941
Cheney, William Fitch	San Francisco, Calif	April 10, 1941
Compton, Marion Lee	Augusta, Ga	March 27, 1941
Dailey, Michael A	M C, U S Army	October 27, 1941
Darling, Ira A	Torrance, Pa	October 10, 1941
Fairbanks, Warren Horace	Freehold, N J	August 5, 1941
Fordham, George	Powellton, W Va	October 4, 1941
Friedenwald, Julius	Baltimore, Md	June 8, 1941
Hall, George Washington	Chicago, Ill	October 25, 1941
Joachim, Henry	Brooklyn, N Y	August 18, 1941
Jones, Austin Byron	Kansas City, Mo	September 3, 1941
Jones, Clement Levi	Springfield, Ohio	August 2, 1941
Kaufman, Isadore	Philadelphia, Pa	August 11, 1941
Kinlaw, W Bernard	Rocky Mount, N C	July 24, 1941
Krauss, Allen K	Providence, R I	May 12, 1941
Lord, Frederick Taylor	Boston, Mass	November 4, 1941
Mohler, Henry K	Philadelphia, Pa	May 16, 1941
Moor, F. Clifton	Tallahassee, Fla	February 18, 1941
Olmsted, George Kingsley	Denver, Colo	June 25, 1941
Page, Wendell Heath	Brownwood, Tex	February 14, 1941
Riley, William Henry	Battle Creek, Mich	August 24, 1941
Stem, Leon Thayer	Sarasota, Fla	May 15, 1941
Strietmann, Wm Hurley	Oakland, Calif	July 14, 1941
Syman, Louis Lawrence	Springfield, Ohio	July 16, 1941
Talley, James E	Lima, Pa	July 3, 1941
Wiener, Joseph	Asbury Park, N J	September 8, 1941
Wilson, W Henry	Iohet, Ill	May 16, 1941

Associates

Kaiser Henry Samuel	Reading, Pa	July 11, 1941
Morgan Mark Tad	M C, U S Army	October 8, 1941
Stephens, Doran J	Rochester, N Y	March 19, 1941

(2) Additional Life Members since the last meeting of this Board (4, making a grand total of 171, of whom 16 are deceased leaving a balance of 155)

Beaumont S. Cornell
Walter J. Wilson Sr
Lillian Lydia Nye
Ira Dixon

Fort Wayne, Ind
Detroit, Mich
St Paul Minn
Stockbridge Mass

Dr Piersol proceeded to report as Chairman of the Committee on Credentials. He reviewed the work of the Committee and the candidates for membership. On motion by Dr Piersol, seconded by Dr Fitz, and regularly carried it was

RESOLVED, that the following group of 132 candidates shall be and are herewith elected to Fellowship (those marked with an asterisk—13—being direct elections, all others being advancements—119—to Fellowship)

Likewise on motion by Dr Piersol, seconded by Dr Fitz, it was

RESOLVED, that the following list of five candidates shall be and are herewith advanced to Fellowship "as of April 19, 1942"

The Committee recommended that 5 of the candidates for Fellowship be first elected to Associateship and their names were presented in connection with elections to Associateship, which follow

On motion by Dr Piersol seconded by Dr Fitz, it was

RESOLVED, that the following 100 candidates shall be and are herewith elected to Associateship in the College

A summary of the recommendations of the Committee was presented as follows by Chairman Piersol

A Candidates for FELLOWSHIP

Recommended for Advancement to Fellowship, 12-14-41	119
Recommended for Direct Election to Fellowship, 12-14-41	13
Recommended for Advancement to Fellowship "As of April 19, 1942"	5 137
	<hr/>
Recommended for Election first to Associateship	6
Deferred for Further Investigation or Material	32
Rejected	6
	<hr/>
	181
	<hr/>

B Candidates for ASSOCIATESHIP

Recommended for Election	94
Fellowship Candidates Recommended for Election first to Associateship	6
Deferred for Further Investigation or Other Credentials	29
Rejected	26
	<hr/>
	155
	<hr/>

On motion by Dr Piersol on behalf of the Committee on Credentials, seconded and regularly carried, a resolution was adopted dropping from the Roster of the College, in accordance with provisions of the By-Laws, the names of 11 Associates who had failed to present the necessary credentials for advancement to Fellowship within the maximum five-year period

The following is an analysis on the candidates elected to Associateship on December 13, 1936, this meeting marking the expiration of the maximum five-year term

Advanced to Fellowship	135
Credentials not presented or inadequate	12
Resigned	5
Deceased	5
	<hr/>
	157
	<hr/>

Dr Piersol then presented and discussed the following communications, which had been reviewed by the Credentials Committee

(1) Dr E V Allen—re South American members

“It was the feeling of the Credentials Committee that at this particular time it is inopportune to do anything looking toward the extension of College membership in South America, and after deliberation, the Committee moved that because of the present great international emergency nothing be done, but the question be laid on the table to be reopened if and when more favorable and peaceful conditions in the various hemispheres exist

(2) Dr LeRoy H Sloan, Governor for Northern Illinois—no action required

(3), (4) and (5)—Letters from Drs Sarah I Morris Harold E B Pardee and Francis M Rackemann (Fellows) regarding the revision of inquiry cards distributed about candidates

“The Committee, after reviewing these communications, was of the opinion that it would be a good plan to modify and revise these cards and add to the card a definite request for specific information The Credentials Committee suggests that the card contain the following questions Is the candidate personally known to you If the answer is ‘Yes,’ please reply to the following questions Is this applicant’s personal qualification satisfactory? Are his personal ethics satisfactory? Are his professional attainments satisfactory? Do you favor his election?”

“On the inquiry card concerning Associates, the following question would be added ‘Do you believe the candidate will qualify for Fellowship within the five-year period?’ The Committee suggests that it confer with the Executive Secretary and adopt a new form”

The report of the Committee on Credentials was accepted as a whole, after President Lee had expressed the appreciation of the Board of Regents to the Committee for its long, hard time-consuming efforts

The Executive Secretary, Mr Loveland, reported

- (1) As directed by the Board of Regents during the past year, 1500 copies of the College History had been reprinted and made available for future needs,
- (2) A completely revised College Directory had been published and distributed to all members The Directory contains the names of

4 Masters
3,465 Fellows
1 202 Associates
<hr/>
4,671 Total
<hr/>

(3) Due to deaths since publication of the Directory, the total membership at the current date, exclusive of new elections is

4 Masters
3 452 Fellows
1 201 Associates
<hr/>
4,657 Total
<hr/>

Dr James L Paulin Chairman of the Committee on Public Relations presented the following report

"This Committee met on December 13, 1941, at 2 00 p m, at the College Headquarters, with Dr Roger I Lee and Dr James E Paullin, Chairman, present The Committee recommends that the following resignations be accepted

Dr James A Butin (Associate), Chanute, Kan
 Dr Frank Bryant Cutts (Associate), Providence, R I
 Dr Morris A Hankin (Associate), New Haven, Conn
 Dr Edward C Humphrey (Associate), Harrodsburg, Ky

On recommendation of the Committee and by regularly adopted resolution, specific cases were disposed of concerned with the dropping from the Roster of 2 Fellows for delinquency in dues of two or more years' standing, the deferment of action on 1 resignation and the waiver of dues for 4 members who are ill and out of practice Another resolution was adopted providing for disciplinary action in connection with charges of unethical conduct and violation of the ethics of the American College of Physicians preferred against a member

"Communications

"The Committee recommends

"The communication of Dr Rudolf Schindler in regard to organization of Gastrosocopy be filed as information,

"That the communication of Dr N W Faxon of the American Hospital Association and the National League of Nursing Education be filed as information

"There being no further business, the Committee adjourned

Respectfully submitted,

JAMES E PAULLIN, *Chairman*
Committee on Public Relations"

On motion by Dr Paullin, regularly seconded and unanimously carried, individual resolutions were adopted approving of each recommendation of the Committee on Public Relations and of the report as a whole

President Lee proceeded with the agenda of the Board of Regents and called for the report of the Committee on Preparedness Dr James E Paullin, Chairman, presented the following report

"The Committee on Preparedness of the American College of Physicians met at the College Headquarters on December 13, 1941 Those present were Dr Ernest E Ions, Dr Roger I Lee, Dr Edward L Bortz and Dr James E Paullin, Chairman

"On December 15, 1940, the Board of Regents of the American College of Physicians appropriated \$2,500 00 to be used by the Medical Committee of the National Research Council in evaluating physicians who had filled out the questionnaire of the American Medical Association stating their qualifications either as internists, pediatricians or general practitioners of medicine The National Research Council thought that this work could be done under the supervision of the College better than directly through the Research Council

"We have received from the A M A the names of 74,096 physicians to be evaluated Of this number we have evaluated 27,950, divided as follows

"We have completely evaluated 11,383 internists,
 5,100 pediatricians,
 1,750 Medical Reserve Officers,
 9,717 General Practitioners

"The large group which we are just now beginning to evaluate consists of 46,092 general practitioners These men, generally speaking, are located in the small towns

and small cities of most of the States, and it is very difficult for our consultants to obtain accurate information concerning them. However, up to the present time, we have information concerning 9,717 of this number. In other words, we have approximately 36,000 of these left to be evaluated.

"In order to accomplish this work it was necessary to purchase the following equipment

1 steel filing cabinet for A C P card file and correspondence	\$ 42 00	
1 typewriter desk	55 00	
2 chairs (1 typist's chair and 1 side chair)	25 94	
1 Royal typewriter (with extra long carriage)	117 05	
2 steel files, 8-drawers each for cards	118 80	\$ 358 79

"We have also had to purchase the following supplies

Office supplies (carbon paper, second sheets, typewriter ribbons, etc.)	\$ 63 55	
Postage and Express	73 97	
Stationery and Printing	168 10	305 62

"To carry on the work, it has been necessary to engage the services of one secretary since the 19th of December, 1940, and one typist for a period of seven months, at a total expenditure of salaries to date of

Jewel Lancaster, December 19, 1940, through Nov 19, 1941	\$1,119 38	
Ruth Hatcher, February 4, 1941, through September 19, 1941	627 50	1,746 88
TOTAL EXPENSES		\$2,411 29
Bank Balance, 12-10-41		88 71
		<u>\$2,500 00</u>

"The Medical Building Company has donated to us the use of the necessary space in its building and has furnished us heat, light, water, without any charge.

"It is the opinion of your Committee that this work which the College has undertaken at this particular moment will be of the greatest value to the Board of Procurement and Assignment Service under the Federal Security Administration. We feel confident that the foresight of the College in making this evaluation possible has prevented a delay of at least six or eight months in our Medical Preparedness Program. From past experience, it seems to me that it probably will take another three or four months to complete our files, and it is recommended that the minimum figure of \$500 00 be appropriated to complete this job.

"As you undoubtedly know, all of the reports which have been made to me have been in confidence. Certain code numbers have been utilized in keeping the identity of the Consultants unknown to anyone except me. This information appears on each individual's card in code. Since all of this information is confidential, it is necessary that the cards be considered in the same manner. In view of this fact, it is recommended by the Committee on Preparedness that the cards, including the filing cabinets that contain them, be turned over to the Regional Office of the Procurement and Assignment Committee, which will be located in Chicago for use by this Committee in obtaining physicians for Military and Civilian duty.

"The Committee on Preparedness wishes to take this opportunity of thanking the Governors of the College, the members of the College, and all of the Consultants who helped so unselfishly in making this part of the program possible. We would also like to thank the American Medical Association for their hearty cooperation in this endeavor.

Respectfully submitted,

JAMES E. PAULIN, Chairman
Committee on Preparedness

STATISTICAL ANALYSIS OF EVALUATIONS

States	Internists	Pediatricians		General Practitioners		Med Res Evaluated
		Evaluated	Data Insuff for Eval	Evaluated	To be Evaluated	
Alabama	101	59		839		133
Arizona	44	19		210		
Arkansas	78	32			611	
California	853	312			3,750	
Colorado	124	52			589	
Connecticut	215	111			787	7
Delaware	15	9		128		2
Florida	156	54			819	176
Georgia	196	105			944	215
Idaho	10	4		180		
Illinois	738	340			3,425	
Indiana	221	105			1,936	
Iowa	169	60		1,294		
Kansas	114	41			716	
Kentucky	135	73		1,044		
Louisiana	167	67		647		208
Maine	37	14		333		5
Maryland	275	122		1,065		16
Massachusetts	529	223			1,577	60
Michigan	396	176			1,771	
Minnesota	310	94			1,278	
Mississippi	73	35			585	93
Missouri	387	127			1,837	
Montana	29	9		191		
Nebraska	110	36			712	
Nevada	6	2			35	
New Hampshire	22	15			270	1
New Jersey	309	209			1,766	25
New Mexico	12	8		166		
New York	2,102	1,019			8,227	150
N Carolina	166	77			750	159
N Dakota	32	8		228		
Ohio	664	276			3,072	
Oklahoma	123	58		700		
Oregon	81	27		547		
Pennsylvania	873	457			4,091	57
Rhode Island	69	37			290	6
S Carolina	76	45		519		108
S Dakota	20	7			216	
Tennessee	173	82			923	286
Texas	372	190			2,108	
Utah	22	19		196		
Vermont	29		12	236		1
Virginia	187	95			997	24
Washington	91		42		821	
West Virginia	98	40			659	
Wisconsin	187	83		1,194		
Wyoming	4	4			117	
D C	183	63			414	18
Totals	11,383	5,100	54	9,717	46,092	1,750

Internists evaluated to date, 12-10-41
 Pediatricians evaluated to date, 12-10-41
 Med Res Officers evaluated 12-10-41
 General Practitioners evaluated 12-10-41

11,383
 5,100
 1,750
 9,717

Total number of physicians evaluated

27,950

<i>We were asked to evaluate</i>	74,096
We have evaluated	27,950
To be evaluated	<u>46,146</u>

(Of this last number approximately 8,000 have been evaluated but the states in which they are listed have not been completely evaluated as yet)

DR PAULLIN "The Board of Procurement and Assignment Service operates under the Federal Security Administration. This Board was appointed by a resolution signed by the President of the United States. We operate under the OPM and the Committee on Health and Medical Care, which is headed by Dr. Irvin Abell, and which is now the policy determining committee under the OPM, ours is the Committee that does the work. The Board of Procurement and Assignment has about ten or fifteen subcommittees which work in conjunction with the Board. This Board is the logical one to receive our reports and the benefits of our work. It is the agency that can use this information with effect. Previously, the Surgeon General of the Army was restricted to a considerable extent because no man could get into the Army if he was thirty-five years or over, except under undue circumstances. We hope to help this Committee in determining the military needs of the Government by establishing a pool of one thousand Reserve Officers. If the Surgeon General sends in a request to the Army for twenty internists, we will send him a list of forty, and from that he can choose men who have said they will volunteer, if he wants two hundred men, we will send him a list of four hundred who are capable of being war surgeons. When he takes them out of that pool, it is our business to keep the pool full all the time. 100 00 his needs will be supplied.

"Along with that, there is an effort to protect the civilian population, to see that moderate medical care is given to those people with a moderate amount of curtailment of some of their activities.

"Thirdly, we are attempting through the Medical Education Committee to determine the hospital and teaching needs of all medical schools and all hospitals, and they are asked to cooperate by cutting their supply of medical officers as low as possible. Since practically all teaching institutions have frozen units, or hospital units which have been frozen up until last Monday, those units are released because war has been declared and all teaching institutions now have been advised that they must revise their list of teaching personnel, eliminate those units that were frozen. Hospital units are now liable to be called to active duty.

"There are a lot of other problems up for consideration. This is a vital question with us, particularly with the College. If you will look very carefully each week in the Journal of the American Medical Association, you will find the details printed out all of this. Every week the deliberations of the Procurement and Assignment Board will be published. The Procurement and Assignment Board will meet next Thursday with the Medical Preparedness Committee of the American Medical Association in Chicago, and after that whatever announcement comes will be available in the next issue of the Journal and we hope at that time to get the machinery in operation for the utilization of this information which the College has already accumulated to speed our national medical defense more rapidly than it has ever been done before and to put the right peg in the right hole."

PRESIDENT LEF "The College has received a great deal of credit through this work by Dr. Paullin. It has been a one-man job. He has devoted a tremendous amount of time and energy to it and as a reward of his services, he is now going to receive a greater burden of responsibility. The College is proud to be represented by Dr. Paullin on this national committee. It must be a great satisfaction to the Regents and every Fellow of the College that this College got started long before the

Government upon this difficult program, and now we are going to see the fruition of that work. Dr. Paullin now has left out of the original appropriation of \$2,500.00 by the College a small sum of about \$89.00. He spent much more than that out of his private purse to say nothing of his time. He has a job to finish up, and if it is agreeable to Dr. Paullin, I should hope that someone of the Regents would be willing to move that a further appropriation of up to \$1,000.00 be given for the continuation of his work.

Dr. Pepper reported that the Finance Committee would have a recommendation to cover this item.

On motion by Dr. O. H. Perry Pepper, seconded by Dr. Charles H. Cocke, and regularly carried, it was

RESOLVED that the location of the cards and files when the work is completed, be turned over to the Regional Office of the Procurement and Assignment Committee, which will be located in Chicago, for use by this Committee in obtaining physicians for military and civilian duty, also that when Dr. Paullin's evaluation office is closed, other fixtures may be disposed of and the money realized thereon returned to the College, also that the Board of Regents conveys its heartiest thanks to Dr. Paullin.

PRESIDENT LEE "At this time, it would seem appropriate to have a report from Dr. O. H. Perry Pepper on the activities of the Committee on Medicine of the National Research Council. Sometimes when that Committee meets, I am not sure whether it is a meeting of the Regents of the College or of the Committee on Medicine, because of the large number of representatives from our College."

DR. PEPPER "Mr. President, I have nothing to report that is not already familiar to the Regents. Our first activities were directly advisory to the Surgeons General in a variety of different fields. We prepared manuals and we wrote the standards of physical examination. The Committee on Medicine has eight or nine subcommittees and the American College of Physicians is widely represented on them. More recently the project that the College started, namely, the giving of money for research service desired by the armed forces, has been taken over by the Government through the establishment of the Office of Scientific Research and Development, with the appropriation of considerable millions of money. The activities of these committees of late have been largely devoted to the evaluation of the many hundreds of research projects that have come in, evaluations of them then to be forwarded to the National Research Council, Committee on Medical Research, under the Chairmanship of Dr. Alfred Newton Richards, where the final decision as to whether funds requested from the Office of Scientific Research and Development for the carrying out of these researches is made. A million or more dollars has already been allocated, and several more millions are available. A constant flow of these research projects is still coming in. Some are initiated by individuals, some by committees that have been cognizant of a need, others have been requested directly by one or another of the armed forces or some division of the Surgeons General's offices. For example, there was a surprising need of information on various aspects of malarial control, malarial treatment and malarial knowledge, and some hundred thousand dollars have been allocated for that. I am not familiar, because of the secrecy that surrounds aviation, tank and chemical warfare fields, with the exact details of their projects, but I do know that considerable sums of money have been allocated there, so that the activities of your Board of Regents on these committees have shifted to this new type of work. No doubt there will be additional fields opening up.

"A new committee on which there are several members of your Regents has just been formed to develop certain new anti-infection agents, study of the problem, and they are being properly tried out.

"This College allocated \$10,000.00 to be used within one year upon recommendation from the National Research Council Committees and approval of the Ex-

Executive Committee of this Board \$5,000 00 was allocated to Dr Cohn's work on purified albumin, blood albumin as a blood substitute in transfusions. That money was made available and has proved very useful and has brought the College much credit. The other \$5,000 00 has not been allocated, and it is now my recommendation that that offer now be considered expired."

President Lee then called for the report of the Advisory Committee on Post-graduate Courses, Dr Edward L. Bortz, Chairman.

DR BORTZ: "Mr President and members of the Board of Regents—soon after your President appointed this Committee, a meeting was called and a skeletal outline of the courses was drawn up, and this outline sent to the Executive Committee of the College and to the Committee on Educational Policy of the Board of Regents, with the request that they make suggestions for alterations, additions or deletions. Upon receipt of the answers, the Committee wrote to the directors that had been selected, and these men returned promptly their acceptances to act as organizers for these courses and made very enthusiastic statements in support of this activity by this College. The work of the Committee got away to a good start. The men promptly got into action and prepared preliminary statements concerning the content of the courses, following which the 'General Bulletin,' or preliminary announcement of these courses, was published. The members of the Advisory Committee have all been very active and have received much help from Dr Hugh J. Moigan and members of the Committee on Educational Policy, and from the College Officers available in Philadelphia. During the last two months, details have been increasing in number to the point where your Chairman practically had to be in daily contact with the Executive Secretary. Many conferences have been held. The General Bulletin was distributed to all members of the College, and within a very short time registrations began coming in. Already at this time, Course No. 1 in Allergy under Dr Robert A. Cooke is filled to capacity, as is also Course No. 10, Internal Medicine, under Dr Cecil J. Watson at the University of Minnesota. Registration in other courses is developing satisfactorily (Dr Bortz then read the number registered for each course).

"Acting on a resourceful suggestion by Dr Francis G. Blake and approved by the Board of Regents, the Executive Secretary is engaged in obtaining advance copies of suggested reading and informal reading lists from each director for publication in an early issue of the 'Annals of Internal Medicine,' in order that all members of the College may be given the benefit of knowing what constitutes the most important and pertinent literature available bearing on these subjects.

"There have been many interesting and flattering comments and letters received by the Executive Office on the work of the College in the field of postgraduate education. Throughout the South, members have decried the fact that there are no courses available during the summer months. This is something for the Regents to study in the future. Just how much influence the present national situation will have on the courses we cannot say, but it is the opinion of your Committee that everything possible will be done to see that these courses are carried through to a successful conclusion.

"Certain thoughts come to mind regarding the possibility of offering opportunities for men in the service, physicians who are not necessarily members of the College, to participate in courses where there is not yet a completed enrollment. We have contacted all the College Governors, asking them to stimulate their local clientles and membership to enroll."

Dr Pepper inquired how the College fares financially on these courses whether the College contributes or gains.

SECRETARY LOVELAND: "Ordinarily the College expends \$500 00 or more beyond the income for these courses. The entire registration fee collected from each member is turned over in full to the director of the course. The College finances the organization of the courses, publication of the bulletin and registration expenses. Last

year one of the Directors, Dr E V Allen, refused to accept the honorarium but the College paid all the local expenses, including guest instructors. However, there was a credit balance created and unused."

PRÉSIDENT LEE "These courses have been in general very extraordinary, and Dr Bortz and his Committee have been very adroit in organizing the different types of courses. As their experience increases, they are finding out what our Fellows really want, and I think eventually they will have some very valuable data. We are very grateful to Dr Bortz for the amount of labor he has put into this. The College is a perfectly relentless boss. It works its people and says occasionally 'Thank You,' but nothing more than that. This is the third Committee that has done a tremendous amount of work—the Committee on Credentials, the Committee on Preparedness and the Committee on Postgraduate Courses. We shall now have the report of the Committee on Educational Policy, Dr Hugh J Morgan, Chairman."

DR MORGAN "Mr Chairman, the Committee on Educational Policy has taken pride in what has been done by Dr Bortz and his Committee, and I would like to point out to the Regents that here in the middle of December there are 145 registrants for these courses. That is something new, something that always has been hoped for—that these courses would be organized and gotten underway before the December meeting of the Board of Regents. Whether or not the war is going to make it difficult for the consummation of the plan is beside the point at the moment. Certainly this Committee has done a splendid job."

"The only other matter that the Committee on Educational Policy would like to bring before the Regents has to do with the efforts that we have made in the past year and a half to make some contribution in the work of continuing education for men in the service. You will recall that at the last meeting the matter of organizing programs to be taken into areas was discussed. Apparently the plan did not meet with wholly favorable acceptance and was abandoned. We are trying to continue operating on that objective. It occurred to us that possibly something could be done about the library facilities of military hospitals where reference books could be made available. In the last war, it was impossible to get any of that sort of thing and no information was available, except by word of mouth from one of the seniors in the service. It was almost impossible to get information at all. Your Committee has been in communication with the Surgeon General's Office, through Captain Davis and Colonel Hillman, and we are informed that there is a basic allowance for the provision of medical journals for hospitals of five hundred beds or larger, service hospitals, and we have been supplied with the list of journals, twenty in number. We immediately discovered that the list did not contain our own 'Annals of Internal Medicine.' Also, there is a list of some sixty or seventy textbooks which constitute the 'basic allowance for books of hospital libraries of hospitals of five hundred beds or more.' The actual type of text and the name of the author are not given in any of these lists, which leads us to feel that some thought directly related to the quantity and quality of the material available would be an important contribution. To that end, your Committee yesterday passed the resolution that 'the Board of Regents authorize the Committee on Educational Policy to communicate with the proper authorities concerning the improvement of medical library service for hospitals of five hundred beds or more.' I would ask the Board of Regents, and I herewith move the adoption of that resolution."

The motion was seconded by Dr Charles H Cocke.

DR PEPPER "Would it not be a good idea to channel that through the Committee on Medicine. It would then carry the weight of a body that is definitely and officially advisory to the Surgeon General's Office. I think the same information would apply to the larger battleships and units of the Navy."

DR MORGAN "I certainly agree, and I will channel it that way."

PRESIDENT LEE "The resolution confines itself to hospitals of five hundred beds or over, and one wonders if it might be possible to have circulating books and circulating periodicals among smaller hospitals. A great many of these five hundred bed institutions are pretty well provided for, and they can do a good deal about looking after themselves, but some of the smaller ones might need a limited amount of help."

DR MORGAN "I will drop 'the five hundred bed designation' and merely say 'service hospitals'."

Dr Pepper brought up for discussion the question of whether the College might make a contribution of sending perhaps one hundred copies of the "Annals" to a hundred places to be designated by the Surgeon General. Dr Morgan and Editor Pincoffs both felt this an expense of some little consequence, and it would be more appropriate to urge the Surgeons General to add the "Annals" to the list of approved journals for service hospitals.

Dr Paullin suggested that the request should be routed through the Procurement and Assignment Division, Committee on Medical Education and Hospitals, with a recommendation of the Committee on Hospitals going directly to the Surgeon General's Office in the War Department.

In this opinion Dr Pepper and Dr Morgan concurred, but pointed out that no change in the resolution would be required, because it reads "to the proper authorities."

The motion was put to a vote and unanimously carried in the following form:

RESOLVED, that the Board of Regents of the American College of Physicians authorizes the Committee on Educational Policy to communicate with the proper authorities concerning the improvement of medical library service in service hospitals.

Dr Hugh J. Morgan, one of the College representatives on the Conference Committee on Graduate Training in Medicine, reported upon the meeting of that Committee in Chicago during May, 1941. About ten out of a long list of hospitals that applied for evaluation and approval as proper places for resident training were approved and subsequently the Committee's report was accepted by the Council on Medical Education and Hospitals of the American Medical Association. Dr Morgan said in part: "In my judgment the Conference Committee constitutes a satisfactory medium for the College to express its interest in and to exert its influence in the matter of evaluation of opportunities for resident training. The Conference Committee is comprised of representatives of the Council on Medical Education and Hospitals, the American Board of Internal Medicine and the American College of Physicians. This arrangement is proving to be a satisfactory one from the point of view of all three groups."

A question was asked concerning the work of the Advisory Council on Medical Education.

DR MORGAN "This Advisory Council has representatives of the American Hospital Association, the Catholic Hospital Association, the State Boards of Medical Examiners, the American College of Surgeons and the American College of Physicians. I cannot say that the Council has yet accomplished very much, but I have the feeling that it has ambitions and I think it would be to the advantage of this College to remain a member, or to retain membership in this Council, until it is observed what the Council is going to do."

DR SPONS "I quite agree with Dr Morgan. There is a process of evaluation going on in that Council, and we may need quite a little help. It is the kind of help we are going to need which would be the kind furnished by the College representation."

President Lee called for the report of the Committee on Fellowships and Awards, Dr Francis G. Blake, Chairman.

DR BEAVER "I shall report first, briefly, on the Research Fellows who have completed their work since the last meeting of the Board of Regents. Dr William

Woods Beckman Dr Lewis Dexter and Dr Morris Tager have completed their fellowships Dr Beckman, who worked under Dr van Slyke at the Hospital of the Rockefeller Institute on the chemistry of sterols, has not yet submitted a final report Dr Dexter, who worked under Dr Houssay at Buenos Aires on various aspects of experimental hypertension, has submitted a final report, expressing his gratitude for the fellowship and the value of the experience in Dr Houssay's laboratory, where all the facilities of the laboratory were made available for his work Two papers embodying the results of his work have been written and will be submitted to the 'Annals of Internal Medicine' Dr Dexter is now at the Peter Bent Brigham Hospital in Boston Dr Tager, who worked under Dr George H Smith at Yale on staphylococcus infection, has made a final report, accompanied by a reprint covering studies on staphylo-lysin, carried out under tenure of his fellowship Dr Tager is now Instructor in Immunology at Yale Dr Homer Swanson, whose resignation on March 1, 1941, has already been reported, has submitted a report that reprints of papers resulting from his studies on Vitamin E deficiency and on fat embolism, under tenure of the fellowship, will be sent as soon as available Dr Swanson now holds a resident appointment at the New York Neurological Institute

"The three fellows appointed at the meeting of the Board, December, 1940, are now at work as follows

Dr William Arrowsmith, since July 1, 1941, under Dr Carl V Moore, Washington University, St Louis, on iron metabolism,

Dr Allan D Bass, since September, 1941, under Dr William T Salter at Yale on hormone factors in neoplastic disease,

Dr Rulon W Rawson, since September 1, 1941, under Dr James H Means at the Massachusetts General Hospital on thyroid physiology

"The Committee on Fellowships and Awards has this year received eleven applications for fellowships for the coming year from men who are graduates of a considerable number of universities—the University of California, Stanford, Wisconsin, Harvard, Columbia, Southern California and the University of Vienna After careful consideration of these applicants, the Committee has selected two whom it considers the two most outstanding of the group

Dr James Hopper—Graduate of the University of California Medical School, 1939, internship and residency with Dr William J Kerr at the University of California Dr Hopper has this year been working on a Cox fellowship at Yale, in the Department of Internal Medicine He is highly recommended by Dr Kerr and also by Dr Mettier of the University of California as one of the outstanding young men of their group that they have had in recent years He has been in New Haven just a short time, and we feel, as far as we can judge at present, that the recommendations of Drs Kerr and Mettier are quite just ones Dr Hopper makes application for his fellowship to engage in studies of blood volume, particularly a comparison of the carbon monoxide and dye methods of various states, to work in the Department of Medicine at Yale under Dr Peters

"The second man that we considered outstanding is

Dr Joseph L Lihenthal, Jr—Graduate of Johns Hopkins, 1937, internship under Dr Walter W Palmer at Presbyterian Hospital, New York City, six months residency at National Hospital, Queens Square, London, and now on the resident staff at Johns Hopkins He is particularly interested in neurological problems, and he desires to go to Vanderbilt University to work under Dr Harvey, who is one of our former fellows of some years ago, who worked in England The particular problems which he wishes to study are those re-

lated to neuromuscular physiology and myasthenia. He is strongly supported by Dr Philip Bard, Dr Walter W Palmer, Dr W T Longcope and several others.

"The Committee on Fellowships and Awards unanimously recommends that Research Fellowships, in the amount of \$1,800 00 each, beginning September 1, 1942, be awarded to these two selectees."

On motion by Dr Blake, seconded by Dr Ions, and unanimously carried, it was RESOLVED, that Research Fellowships in the amount of \$1,800 00 each shall be awarded, beginning September 1, 1942, to Dr James Hopper, Jr, whose home is in San Francisco, Calif, for work concerned with a comparison of the carbon monoxide and dye methods of blood volume determination under Dr John P Peters of Yale University School of Medicine, and to Dr Joseph L Lilienthal, Jr, Baltimore, Md, for work concerned with observations on myasthenia gravis and related problems in neuromuscular transmission in man under Dr A M Harvey in the Department of Medicine at Vanderbilt University School of Medicine, Nashville, Tenn.

DR BLAKE "The Committee on Fellowships and Awards held long discussions and experienced considerable difficulty in picking the above two men over two others in the group of eleven, who, perhaps, are almost equally good in accomplishment and promise, and so, after discussion, the Committee wishes to recommend, if it is agreeable to the Regents and the Finance Committee, that a third fellowship be awarded to Dr Charles P Emerson, Jr, Graduate of Harvard Medical School, 1937. His hospital training was at Boston City Hospital and at the Thorndike Laboratory. He is highly recommended by every one who has written about him—Keefer, Finland, Castle and others. He wishes to continue and carry along further investigations, and is now concerned with the physical and chemical studies of red blood cells, particularly in relation to problems of hemolytic anemia under Dr William B Castle at the Thorndike Memorial Laboratory, Boston.

"Again the Committee unanimously recommends the granting of this fellowship."

On motion by Dr Blake, seconded and regularly carried, it was

RESOLVED, that a Research Fellowship, in the amount of \$1,800 00, beginning September 1, 1942, be awarded to Dr Charles P Emerson, Jr, for work concerned with the study of various factors which act in vitro as hemolyzing agents and in animals and man to cause hemolytic anemia under Dr William B Castle, Dr George R Minot and Dr T H Ham at the Thorndike Memorial Laboratory, Boston City Hospital.

(Secretary's Note: Dr Emerson was unable to accept this fellowship due to summons to active military duty with the Harvard Base Hospital, but provision was made that he may file application to resume the fellowship following his discharge from service, and that such application will receive special consideration.)

DR BLAKE "The Committee on Fellowships and Awards, recognizing that in all probability there may be withdrawals of fellows appointed prior to assuming of fellowships because of call to service with the armed forces, discussed the question of recommending the appointment of a fourth very good man as an alternate, in awarding to him a fellowship to take effect should one of the appointed fellows withdraw prior to the assumption of the fellowship. This fourth man is

Dr Carl G Heller—Graduate of the University of Wisconsin, M.D. and Ph.D., 1940. His hospital training was received at the Wisconsin General, Madison. He is now in Detroit at Wayne University with Dr Gordon B Myers. All during his period of study at Wisconsin, both for his Ph.D. and M.D. degrees, he was actively engaged in research largely with Dr Scavringhaus.

and has to his credit a number of publications with Dr Sevringhaus and later two or three of his own dealing with hormone problems along general lines of work in which Dr Sevringhaus has been interested. He is highly recommended by Dr Sevringhaus, Dr Henry R Carstens, Dr Gordon B Myers and Dr Walter J Meek. He seems to be a man of industry and lots of drive, described as a very competent individual. He desires a fellowship to work on the physiological problems of hypo- and hypergonadism in relation to hypo- and hyperpituitarism in human males and females under Dr Myers at Wayne University.

'The Committee again unanimously recommends the award of this fellowship to Dr Heller as an alternate.'

On motion by Dr Blake, seconded by Dr Pincoffs and regularly carried, it was **RESOLVED**, that a Research Fellowship of the American College of Physicians, in the amount of \$1,800.00, beginning July 1, 1942, be awarded to Dr Carl G Heller as an alternate should there be withdrawals of other appointed fellows, this fellowship to be made for work concerned with the physiological problems of hypo- and hypergonadism in relation to hypo- and hyperpituitarism in human males and females under Dr Gordon B Myers at Wayne University, Detroit.

On motion by Dr Blake, seconded by Dr Cocke, and regularly carried, it was

RESOLVED, that if during the tenure of his Research Fellowship a fellow resigns because of entrance into service in the armed forces, when such service is completed an application for resumption of his fellowship shall receive special consideration.

DR BLAKE "With respect to the Phillips Memorial Award, letters were sent out about the first of November to all Regents and Governors, and to a selected list, as has been done in the past, asking for suggestions and nominations of at least three individuals, arranged in the order of choice, for the Phillips Memorial Award. From this canvass, the Committee received fifty-three nominees over which considerable time has been spent, combing out those who obviously were not very satisfactory nominees and reducing the list down to about fifteen for further consideration. After reviewing the accomplishments and the pertinence of the work of these individuals, taking into consideration the fact that the Award is for work in Canada or in the United States, relatively recent work, either in the field of Internal Medicine or the basic sciences, having relation to Internal Medicine, the Committee on Fellowships and Awards unanimously recommends to the Board of Regents that the John Phillips Memorial Medal for 1942 be awarded jointly to Dr John Rodman Paul, Professor of Preventive Medicine, Yale University School of Medicine, and Dr James Dowling Trask, Associate Professor of Pediatrics, Yale University School of Medicine, for their studies on the clinical epidemiology of poliomyelitis, and more particularly for their recent demonstration of the prevalence of the virus of poliomyelitis in feces and its detection in sewage and in flies.

"Dr Paul was born in Philadelphia, Pa., on April 18, 1893. He received the degree of Bachelor of Arts at Princeton University in 1915 and the degree of Doctor of Medicine at Johns Hopkins University in 1919. He was Assistant in Pathology at Johns Hopkins during 1919-20 and interne at the Pennsylvania Hospital, Philadelphia, from 1920 to 1922. He was Director of the Ayer Clinical Laboratory, Robert Robinson Porter Research Fellow in Medicine and Associate in Surgical Pathology at the University of Pennsylvania from 1922 to 1928. Since 1928 he has been a member of the faculty of Yale University School of Medicine as Assistant Professor of Medicine from 1928 to 1934, Associate Professor of Medicine from 1934 to 1940 and Professor of Preventive Medicine since 1940.

"Dr Trask was born in Astoria, Long Island, N. Y. on August 21, 1890. He received the degree of Bachelor of Philosophy at Yale University in 1913 and the

degree of Doctor of Medicine from Cornell University in 1917. He was an interne at the Bellevue Hospital, New York, from June, 1917, to May, 1918, and served in the U S Army during the World War I, from May, 1918, to December, 1919. He was Assistant Resident Physician at the Hospital of the Rockefeller Institute for Medical Research in New York from 1919 to 1921, Instructor in Medicine at Yale University School of Medicine from 1921 to 1925, Assistant Professor of Medicine from 1925 to 1927, and since 1927 has been Associate Professor of Pediatrics.

"Begun a decade ago at a time when research on poliomyelitis had for many years been more concerned with the experimental disease in monkeys than the natural disease in man, Paul and Trask's earlier work was concerned with studies on the epidemiological, clinical and immunological aspects of abortive poliomyelitis. As a result of these investigations they emphasized the much greater prevalence of the minor or Wickman type of abortive poliomyelitis than had previously been suspected and the probable significance of this generally unrecognized prevalence of minor infections in the spread of the disease. In subsequent work they established the importance of employing recently isolated strains of virus in studying the immunology and pathogenesis of poliomyelitis. Their more recent investigations have been particularly concerned with the method of transmission of the disease. In the course of this work they have shown that monkeys may be successfully infected subcutaneously, intraperitoneally and by way of the gastro-intestinal tract much more readily than had been supposed, that the virus is more easily and frequently recoverable from the stools than from the nasopharynx in both paralytic and abortive cases, and that it is present in the feces not only during the acute stage of the disease but also for weeks after recovery from the acute phase. They have, furthermore, shown that the virus may be isolated from sewage during the course of epidemics, and quite recently have detected its presence in flies collected in the field during epidemics of the disease.

"Undertaken at a time when poliomyelitis was generally if not universally believed to be a contact infection transmitted by way of the upper respiratory tract, Dr Paul and Dr Trask's studies of the disease have not only served to reopen the whole question of the epidemiology of poliomyelitis but have also marshalled an impressive body of evidence which would appear to support the idea that poliomyelitis may after all be an 'intestinal disease'."

On motion by Dr Morgan, seconded by Dr Pincoffs and regularly carried, it was

Resolved, that the recommendations of the Committee on Fellowships and Awards be approved and that the John Phillips Memorial Medal be awarded for 1942 jointly to Dr John R Paul and Dr James D Trask, medals to be awarded to each, the names of both recipients appearing on each medal.

Dr Morgan suggested that the College obtain photographs of all Phillips Medalists for record in the College Archives. Secretary Loveland replied that photographs have been obtained of all previous recipients.

President Lee called for the report of the American Board of Internal Medicine, Dr Ernest E Irons, Chairman.

Dr Irons said he had no formal report to offer, but that the work of the Board is proceeding satisfactorily.

Dr PEPPER "How have the specialized examinations worked out?"

Dr IRONS "In general one could say that the system has been satisfactorily established. The tendency will be, I think, for a very much smaller number of holders of the certificates of the Board to want also some sub-specialty designation. I do not have the figures exactly in mind but perhaps of all those who are in Cardiology—we circulated at the request of that group—not over ten per cent of them wanted to have another additional tick on the bottom of their certificates. I think as time goes on it will appear that this rising demand for sub-specialization will subside. Of course the people who are especially interested in one of these sub-specialties will not be

particularly enthused over this tendency. The Board has made no effort to influence the matter one way or another. Four sub-specialties are now being covered by the Board. We are also going to have a number of requests for recognition of further sub-specialties. The feeling of the Board is that those requests will have to be scrutinized very carefully, and I suspect the Board will move very slowly in the immediate future in these directions.

President Lee called for the report of the Committee on Annals of Internal Medicine, Dr. Walter W. Palmer, Chairman.

DR. PALMER: "As may be seen from the financial statement, the ANNALS is more than self-sustaining. For Volume XIV the surplus was nearly \$7,000.00 (\$6,947.86). The character of the articles has improved steadily. Your Committee believes the publication of the ANNALS is one of the important functions of the College.

'With the increase in costs of publication the need for reducing the number of pages printed may occur. For the present, your Committee recommends no change be made in the size of the journal.

"The Editor reports a request from a journal called *Medicas*, published in Spanish in New York and distributed to South American countries, to republish entire articles appearing in the ANNALS. It has been the policy of the ANNALS not to permit the publication of entire articles. Most requests for this privilege come from commercial journals. Some consideration to the request on the part of *Medicas* seemed desirable, in view of the good neighbor policy. However, for the present, it would appear wise not to recommend any exception to the general policy until the publication, *Medicas*, has been thoroughly investigated."

President Lee then asked for a report from the Editor of the ANNALS OF INTERNAL MEDICINE, Dr. Maurice C. Pincoffs.

DR. PINCOFFS: "Mr. President, I have very little to report. In accordance with the decision of the Committee on the ANNALS at its last meeting, the journal is now appearing in two volumes a year, each with its own index. The first of these half-year volumes will come out at the end of December. I might say a word in amplification of the question of economy in the ANNALS during the war period. It is quite well realized, with a possible falling off of subscriptions and a probable rise in cost of publication, that the time will come when the size of the ANNALS will have to be reduced, in order to keep from having a deficit. It is, however, so strongly on the credit side at the present time, that it is felt that it will not be necessary to inaugurate a policy of economy in advance of possible handicaps later on. Upon the authority of the Executive Committee of the College, such a reduction or change in policy could be made in the mid-year, or at any other time that would be advisable, if that condition should arise."

Secretary Loveland reported that no immediate problems could be foreseen. The present publishing contract extends through June, 1942, and there have already been purchased adequate paper stock and envelopes for the period ending June, 1942.

DR. PEPPER: "I can think of nothing more useful for this College to do than to go into the 'red,' if necessary, in maintaining the present standard of the ANNALS. It would be a mistake to let the decision on the ANNALS be determined by the mere bookkeeping item. We have had a surplus every year for some time. There is no reason to think that we are not going to go on having it, and I would think that the present situation is one where we ought to move forward rather than backward, even if we used some considerable parts of our surplus. With this thought in mind, I recently wrote to Editor Pincoffs and urged him to introduce colored illustrations, which will come into medical publishing as they become better and cheaper, and my thoughts run along that line rather than that of retrenchment."

The meeting at this point recessed at 12:55 p.m. for luncheon.

At the resumption of the meeting, President Lee called for the report of the Committee on Survey and Future Policy. Dr. James E. Paullin, Chairman.

"The Committee on Survey and Future Policy of the American College of Physicians met at the College Headquarters on December 13, 1941, with the following in attendance: Dr Charles H Cocke, Dr Jonathan C Meakins, Dr James Alex Miller, Dr Hugh J Morgan, Dr George Morris Piersol, Dr Maurice C Pincoffs and Dr James E Paullin, Chairman

"Your Committee on Survey and Future Policy wishes to submit this report to the Board of Regents

"A communication from the National Committee to Signalize Benjamin Franklin's Continuing Contribution to American Civilization is read with a great deal of interest. It is recommended that the American College of Physicians cooperate with this Committee and express our willingness to lend whatever documents, historical papers and the like which may come into our possession for the furtherance of the purpose of the Committee,

"A communication from Dr Maurice A Schmitker, of Toledo, Ohio, President of the American Federation for Clinical Research, requesting that there be a combined or joint meeting of his Society with the American College of Physicians, has been received. It is recommended that we welcome the American Federation for Clinical Research and extend to them an invitation to attend the Morning Lectures and General Sessions of the meeting of the College in St Paul, April 20-24, 1942. We further suggest that the meetings of the American Federation for Clinical Research, which are contemplated to be held in Minneapolis, take place before the meeting of the College in St Paul. We feel that the establishment of a friendly relationship with this organization to be beneficial, both to the College and to the organization.

"At a meeting of the Board of Regents on April 22, 1941, a resolution was adopted as follows:

"RESOLVED, that the recommendation of the Committee on Survey and Future Policy, concerning the waiver of dues of members called to active military service, be referred back to said Committee for study and report at the December, 1941, meeting of the Board of Regents

"In view of the fact that the emergency has passed and that War is now declared, it is recommended to the Board of Regents that all members of the American College of Physicians who are on full-time duty with the armed forces, or who are assigned to other full-time duties concerned with national defense, have their dues reduced to correspond with those which are now effective for those members who are now officers of the Army and Navy, namely \$10.00 per annum.

"It is also recommended that the Board of Regents address a communication to the Procurement and Assignment Board of the Federal Security Administration, attention of the Sub-committee on Medical Education, stating the gratification which comes to the Board of Regents of the American College of Physicians for the proposed program outlined by the Sub-committee for the continuance of medical education of medical officers now in the armed forces as outlined and operative at the present time. The American College of Physicians wishes to offer its full cooperation and assistance in furthering the continuance of the educational program as outlined with the hope that this objective will be applicable to all Station and General Hospitals.

"In view of the present emergency, your Committee feels that modification of the present program of the American College of Physicians and any suggestions for new activities should have careful and mature study. It is suggested that any action towards a change in any of these policies be considered a responsibility of this Committee and, in view of the present emergency, that that Committee study thoughtfully and carefully the activity of the College in order to report regularly these activities to the Board of Regents.

Your Committee approves the suggestions and recommendations of the Committee on Educational Policy and its recommendations concerning the improvement of the Station and General Hospitals.

"In view of the fact that the United States at the present time is at War, it is highly important that the American College of Physicians continue its close relationship with its members, that it use its influence in exerting every effort toward the preservation of American institutions and the high ideals for which the American College of Physicians stands. It is contemplated that this College will carry on its activities as best it possibly can under the present emergency conditions. It is conceived that certain inevitable circumstances may arise which may curtail certain of our activities, but those activities may be curtailed in amount, but not in principle. It is believed that the Postgraduate Courses as outlined by our Committee are feasible and quite worth while. We hope that our program will continue along the high standards which have been established over this long period of years. Nothing else would be in keeping with the traditions which have been established by those who have gone before in this our organization.

Respectfully submitted,

JAMES E. PAULLIN, *Chairman*
Committee on Survey and Future Policy"

By resolution, the above report was adopted seriatim and in its entirety.

President Lee called for the report of the House Committee, Dr. William D. Stroud, Chairman.

DR. STROUD: "The three paintings in the series, 'Pioneers of American Medicine,' entitled 'Beaumont and St. Martin,' 'Osler at Old Blockley' and 'The Conquerors of Yellow Fever,' were loaned to the College Headquarters through the courtesy of John Wyeth and Brother, in order to show what has been accomplished and can be done in producing original paintings depicting some epoch in American Medicine.

"No report has yet been received from the American Physicians Art Association, through which Dr. E. E. Woldman, F. A. C. P., Cleveland, offered a prize for the production of a painting acceptable to the College. However, no adequate time has yet elapsed, because the offer was made only in the spring of 1941, and the Association has not since held a meeting.

"*The College Headquarters*—There is nothing in particular to report, other than the fact that the Headquarters has been maintained in excellent condition with minor improvements here and there. Financial report for the year 1941 will show that the total cost of the Headquarters, including janitorial services, all equipment for the Executive Offices, maintenance, heat, light, gas and water, insurance and taxes, will be somewhat less than \$5,000.00. We may reasonably expect some increase in maintenance with War conditions and higher prices of fuel. During the coming year the exterior woodwork should be painted. During the past summer, a further reduction in real estate assessment on the College Headquarters has been obtained, namely, from \$39,700.00 to \$30,200.00. At the time the Headquarters was purchased in 1936, the assessment was \$65,000.00.

"*404-12 S. 42nd Street*—The adjoining property, extending to Osage Avenue from the College line, was purchased on July 11, 1941, with the approval of the Executive Committee of the College. The purchase price was \$9,000.00, but the additional costs for taxes, settlement, commission, etc., brings the total expenditure to \$9,540.28. The property was assessed at \$23,300.00 at time of purchase, but this assessment has since been reduced to \$17,200.00. It has been the hope of the House Committee that this property could be resold at book value to the National Board of Medical Examiners and the American Board of Surgery for their headquarters, thus establishing a small 'medical center' here. Although there have been numerous meetings and inspections, no definite developments have been reported to date."

President Lee called for the report of the Committee on Advertisements and Commercial Exhibits, Dr. George Morris Piersol, Chairman.

"DR PIERSOL "This Committee has not met, but our deliberations have been carried on largely by mail and telephone. We have passed upon a number of requests for exhibit space at the Annual Meeting. The difficulties, so far as advertising in the ANNALS is concerned, are not great, because we follow certain regulations already adopted by our Committee and apply the rules of the Council on Pharmacy and Chemistry of the American Medical Association to pharmaceutical advertisements. The Committee, in certain instances, has gone further in its restrictions on advertisements than most other medical journals, including those published by the American Medical Association. In spite of opportunities to accept very advantageous advertising contracts, as for example a double-page spread monthly of a cigarette advertisement, the Committee has refused the contracts, because it has considered them irrelevant to the practice of Internal Medicine and derogatory to the dignity of the journal."

President Lee requested report from the Treasurer, Dr William D Stroud

DR STROUD "The income of the College for 1941, with estimations for the month of December, will be approximately \$116,000 00, \$3,000 00 more than estimated. The gross expenditures for 1941, also with estimations for December, will be approximately \$92,000 00, leaving a surplus of about \$24,000 00. The College operated at approximately \$9,000 00 below its budget.

"The book value, or purchase price, of its security holdings is

Endowment Fund	\$120,763 57
General Fund	93,034 72
	<hr/>
	\$213,798 29, Total

"The present cash value of these securities was on December 11 1941, \$206,381 88, or a depreciation of only slightly over \$7,000 00.

"The College employs a competent firm of investment counselors at a relatively small cost of about \$400 00 per annum, and receives frequent surveys of its security holdings, which are reviewed periodically by the Finance Committee of the College.

"We believe the financial condition of the College sound and satisfactory. The accounts, as usual, will be audited by a certified public accountant at the end of the year, and his statements published in the ANNALS."

On motion by Dr Cocke, seconded by Dr Pepper and regularly carried, the Treasurer's report was accepted and filed.

President Lee then called for the report of the Finance Committee. Dr O H Perry Pepper, Chairman.

"The Finance Committee of the American College of Physicians met at the College Headquarters on December 13, 1941. Drs Bruce and Pepper of the Committee were present, Dr Stone being delayed on account of bad weather. The Treasurer and Executive Secretary were also present.

The Committee begs to report

- (1) Drexel & Co have proved satisfactory Investment Counselors and Custodians. Their charge has been \$425 00 a year less than our previous advisers.
- (2) The Finance Committee recommends that no change be made in the present rules for dues of members entering active service in the armed forces. At present such officers pay \$10 00 a year, as do the regular officers of the Army and Navy. Attention of the members will be drawn on the bills and in the ANNALS of their right to have any individual case considered by the Regents.
- (3) One such case is that of Dr H B Kirkland, of New York City, who has received the waiver of his dues during the term of his service with the American Heart Association. The Finance Committee recommends the waiver of his dues for the period

- (4) A year ago the Regents made available for one year \$10,000 00 for research desired by the Army or Navy. One-half was allocated to Cohn of Harvard for work on blood substitutes. The remaining \$5,000 00 has not been allocated. In view of the fact that adequate funds for medical research have been appropriated by the Government, the Finance Committee recommends that the Regents declare the term of the offer expired and so notify the National Research Council.
- (5) Also an appropriation was made a year ago to finance the work of Dr. Paullin in evaluating the self-designated internists of the country. This extremely valuable work has now been extended to the whole field of the practitioners of medicine. The sum appropriated last year has been expended, and the Finance Committee recommends that an additional \$1,000 00 be made available to Dr. Paullin for the completion of this task.
- (6) The Finance Committee reports that figures supplied by the Executive Secretary show that of the more than \$32,000 00 in closed banks in Pittsburgh, all but \$1,391 19 has been recovered.
- (7) Without going into details, the Finance Committee wishes to inform the Regents concerning the suggestions of Drexel & Co., dated December 11, 1941.

- (a) That the College sell some \$25,000 00 railroad and utility bonds and purchase \$25,000 00 additional Defense Bonds. The bonds to be sold form almost one-half of our non-governmental bond holdings of about \$55,000 00. While we already hold \$62,000 00 governmental bonds, the exchange suggested could be carried out with a slight gain over original prices, but with a loss of annual income of some \$350 00.

The Committee did not approve the suggestion, feeling that it was quite proper to hold in a total account of about \$214,000 00, about one-quarter in bonds of this general character.

The Committee approved the recommendation for the sale of our holding of preferred stock of the Central New York Power Co.

No changes were suggested in the common stock group. Drexel & Co.'s advice on the holding uninvested of most of the \$22,000 00 cash balance was approved.

- (8) The Finance Committee recommends to the Regents the approval of the budgets prepared by the Executive Secretary for the year 1942, with the addition of \$1,000 00 for the evaluation task of Dr. Paullin. The total budget requests for 1942 equal \$86,176 50, plus the \$1,000 00 for Dr. Paullin, \$87,176 50. This, compared with the 1941 budget of \$100,644 00, is \$13,467 50 less.

The explanation of this difference lies chiefly in three items in the 1941 budget:

- (a) \$10,000 00 appropriated for research, (b) \$2,500 00 to Dr. Paullin, (c) over \$700 00 for purchase of new addressograph.

Other changes deserving mention include a further reduction in the taxes on the College Headquarters, and suggested increases in salaries for the Headquarters, totalling \$710 00 and an increase of \$1,700 00 in the estimated cost of publication of the ANNALS.

The expenditures for 1941, with December estimated, show close adherence to the budget figures.

The expected surplus for 1941 is \$24,193 25. The Finance Committee recommends the salary increases suggested by the Executive Secretary and the adoption of all the suggested budgets.

The Executive Secretary will be glad to present any desired details.

- (9) The Finance Committee should report that it gave its approval of the investment of a part of surplus funds in the purchase of the house and property adjoining on the south the present College Headquarters.

The price was \$9 000 00 and taxes, insurance, etc. brought the all-inclusive price to \$9,540 28 Reduction in tax assessment has already been obtained

The Finance Committee recommends that no hasty sale or decision be made in the disposition of this property Offers received would net the College a small profit, but the purpose of the purchase was more to insure the control of the future dignified disposition of this neighboring property

- (10) The Committee recommends to the Regents the appropriation of \$50 00 from this year's funds to Mr M R Wiley, the houseman of the College Headquarters, as a bonus
- (11) The Committee also recommends to the Board of Regents an appropriation of \$100 00 for secretarial expenses for the Advisory Committee on Postgraduate Courses

Respectfully submitted,

JAMES D BRUCE

CHARLES T STONE

O H PERRY PEPPER, *Chairman*

Committee on Finance

By resolution regularly carried, the report of the Committee on Finance was adopted seriatim and in its entirety

Dr Lee called for a report of the Committee on Constitution and By-Laws Dr Ernest E Irons, Chairman

Dr Irons had no report

At this point, President Lee reported upon the arrangements for the forthcoming Annual Session of the College in St Paul, saying that activities were going on apace and that if the Regents had any desire to modify the program or arrangements they should consider them at this time He expressed the opinion that the College should continue to function in its ordinary fashion, and he, as President, saw no reason why the College should not proceed in the usual manner with all arrangements

At this point, Dr Lee introduced Dr John A Lepak, General Chairman of the St Paul Session

DR LEPAK "Mr Chairman and members of the Board of Regents, immediately upon the selection of St Paul as the meeting city for 1942, the President and the Executive Secretary conferred with me and we all started immediately in preparing the future plans Before I returned to St Paul from the Boston Session, I had an opportunity to meet many of the experienced officers from former meetings of the College and some of the Governors, and thus obtained some advance information as to how to proceed On return to St Paul, we immediately organized our committees on the same pattern they had been organized previously, with some minor changes We then wrote a letter to each member of the Board of Governors and of the Board of Regents to determine if he would participate in a clinic and what subject he would select In a very short time, forty-four acceptances were received We then organized the men in St Paul Minneapolis, Rochester and some from Wisconsin and elsewhere and in a short time our clinic program was well organized As for the panels, I appointed a chairman who selected a few out-of-town men for the panel program and soon had that program completed We selected five hospitals in St Paul, with a capacity of 1,600 seats daily and added the University Hospital and the College of Science Building next to the University, with an additional seating capacity of 500 seats, so we have available accommodations for 2,100 men at the clinics daily

Our Auditorium is one of the best Auditoriums in the United States, and in it we have ample space to seat 2,800 people for the General Sessions We have adequate room for exhibits, panel programs and also a restaurant, so that attendants may not have to leave the Auditorium

Dr Lepak then read portions from his clinic program, saying it was a fair sample of the program for one day. He likewise read a portion of the panel program, and outlined the general program for entertainment and other activities.

President Lee thanked Dr Lepak for his labors and congratulated him, on behalf of the Regents and himself, for the excellency of the program organized.

Continuing, President Lee said, "The obligation of the President has been to secure the papers for the General Sessions, the Morning Lectures and the Convocation Address. For the latter, we have secured Dr William de B MacNider, whose subject will be 'A Consideration of the Factor of Change in the Animal Organism'. The Morning Lectures we have attempted to make provocative, and we have taken as a general title 'Medical Horizons'. Those who will give lectures we have asked not to be didactic, but rather to attempt to look at the horizons and perhaps a little bit beyond the horizons, to be imaginative and stimulating. It is practically necessary and very fitting, of course, that one of the men to deliver a Morning Lecture should be Dr Cohn, who received the grant of money for research from the College. Exactly how much he will be able to say concerning his particular researches is not yet known, but it is assured that he will have something interesting."

Dr Lee read portions of his program of General Sessions and summarized his arrangements. A new feature, as a precautionary measure against some speakers being unable to attend, Dr Lee had established a group of papers under the title "To be read if time permits." He expressed the intention to follow the general procedure of the College from former years, and said that papers would not be presented unless the speaker himself were present. He expressed optimism toward the prospects of a very successful meeting in St Paul, and assured the Board that the program would be of very great scientific and professional excellence.

President Lee then asked for the report of the Executive Secretary.

SECRETARY LOVELAND "My report is restricted to arrangements for the St Paul Session. The customary business arrangements, including those for meetings of the various Boards, the exhibit, etc, have been made. While there has been no advance indication of dropping off of the exhibitors, it is quite possible that because of the location and the War developments, the exhibit may be slightly smaller. The Officers, Regents and Governors of the College will be housed at the Hotel Lowry, but both the Hotel Lowry and the Hotel St Paul have been appointed joint headquarters, in order that a fairly adequate number of rooms shall be available to accommodate all in attendance."

President Lee asked for a report from the Marshal of the Convocation, Dr Reginald Fitz.

DR FITZ "Mr President, I am sorry to say that my hypersensitiveness to having the names of the newly elected Fellows read aloud is apparently something to which I must get accustomed. After the meeting last year, I thought it would be wise if I could get some evidence on the matter, and accordingly I sent letters asking various gentlemen whether they did or did not like to hear the names read. 372 replies were received, of these 60 per cent felt that a substitute should be devised for the reading aloud of the names, and 40 per cent voted that the names should be read aloud as heretofore. There seemed to be no particular prejudice one way or the other, but what did impress me more than anything else were the letters that came in from several people defending the reading aloud of the names. I have brought two of those letters which I wish to present. The first is from a younger man, inducted a few years ago

'My thought on this matter is that this meeting is designed particularly for the benefit of the newly elected Fellows and to impress them with the significance of their entrance into the College. This should be an event to be remembered, and from my own experience, I can assure you that it was much more impressive to hear my own name read there before a large assembly as a newly-elected Fel-

low of the College than it was to hear the out-going President review the history of the College, a procedure which has been done so often that everybody knows it by heart, or hear the speakers discuss some subject in which none of the newly-elected members are interested'

"The second expresses about the same idea, making a point that to a good many of the younger men the Convocation and the presentation of their names are obviously an event worth while, and because of that feeling, I am convinced the only thing to do is to keep on with reading the names, but to try to do it better than ever before"

DR PEPPER "Since Dr Fitz has been interested in the Convocations they have improved markedly He has accomplished much"

At this point, President Lee brought up the matter of the Regents-Governors Dinner It was announced that the customary Dinner would be tendered on the part of the College to the Officers, Regents and Governors, with a limited number of guests, on Sunday evening, April 19, at St Paul before the formal opening of the Session At these dinners the President presides and matters of particular interest to the College are discussed

Dr Cocke, Chairman of the Board of Governors, reported to the Regents that the College Governor for Maine had offered to resign because he had been called to active military service, but stationed not far from Portland Dr Cocke had advised him that so long as he could still function as Governor, he should continue

PRESIDENT LEE. "There is a somewhat incongruous situation in regard to two committees—the Executive Committee and the Committee on Survey and Future Policy The Executive Committee has been a sort of an ad interim committee, theoretically composed of men within a short distance of the College Headquarters When the Executive Committee meets and votes, it is more often done by mail, and it does not appear, at least to me, that this is quite a valuable function, yet the Executive Committee is empowered with practically all the authority of the Board of Regents, with the exception of electing new members and adjusting fees and dues It has seemed to me that, as in other businesses, the Executive Committee ought to be the Committee of Survey and Future Policy It should be the steering committee It should be the committee that builds up the agenda for the two meetings of the Board of Governors It might have an occasional meeting, or it could transact emergency business by telephone or by correspondence These are some reflections that I indulged in when I had to appoint these two committees, the Executive Committee and the Committee on Future Policy, and while I am out of order in making these remarks, and I will not make any motion I would like to know what the Board of Regents thinks about it Any action taken would not become effective until the committees are appointed at the next Annual Session If the Regents feel inclined to amalgamate these two committees into a real Executive Committee, it would seem better administration to me."

DR STODD Mr President—I would like to move that these two committees be combined with instructions that the Executive Committee become active in the future policy and planning of the College"

DR PEPPER I would like to ask the Executive Secretary to read that part of the Constitution or By-Laws which govern the composition of the Executive Committee"

Secretary Loveland read the section from the By-Laws

DR PEPPER The chief change would be the omission of certain individuals who have continued their interest in the College after their term of service on the Board of Regents has of necessity, expired That may not be a strong argument, and except for that I think the scheme is a very good one This is the only drawback The duties of the Executive Committee with regard to survey and future policy are implied in the wording of the By-Laws It is a perfectly reasonable and normal thing to suggest a change of the kind and I thought that it would change or all except

members of the Board of Regents I do not know whether it is a good idea to have retired Regents stay on the Survey Committee, but that is what we have done They have sort of grown into the position like senior statesmen "

DR STROUD "My original motion was not seconded, so I should like to change it, namely, that a resolution be presented at the next meeting of the Annual Business Meeting outlining the duties of the Executive Committee and, if necessary, enlarging the Committee, not limiting it to the Board of Regents, and providing for its appointment by the President rather than by the Board of Regents "

DR PEPPER "I will second Dr Stroud's motion "

SECRETARY LOVELAND "I believe it would be a mistake to change the personnel of the Executive Committee, adding men outside of the Board of Regents There have been in the early years of the College many occasions when there was real serious work for the Executive Committee, and those occasions might arise again With a mixed membership, some of whom are inexperienced in the work of the Board of Regents, it might prove a rather serious objection Probably Dr Piersol and some of the other men who were active fifteen or so years ago will remember that the whole reorganization was brought about not in the Board of Regents, but in the Executive Committee Those changes and reorganization plans could not have been carried through effectively in the Board of Regents as then constituted, but it was accomplished in the smaller and more effective Executive Committee I feel that your present Constitution and By-Laws should not be altered I am wholly favorable to assigning the duties of your Committee on Survey and Future Policy to your Executive Committee The Executive Committee as now constituted is a protection, although it may not be called upon to function "

On investigation of the present personnel of the Committee on Survey and Future Policy, it was found that no member would be affected by the change other than Dr James Alex Miller It was further learned that the organization of the Committee on Future Policy and Survey was not set up in the By-Laws, but under resolution of the Board of Regents

Dr Stroud withdrew his motion and Dr Pepper his second Dr Piersol pointed out that the correction of the present fault is simple and that all that would be necessary is to disband the present Committee at the end of the present year and refer all such matters in the future to the Executive Committee

Dr Fitz suggested that the Executive Committee could be nominated by the regular Nominating Committee, rather than directly elected by the Board of Regents Dr Cocke pointed out that that would require amendments to the By-Laws Dr Morgan expressed doubt as to whether the existence of the two Committees had caused the College to suffer in any respect, and said there appeared to be no very pressing reason for making the change at this time

On motion by Dr Piersol, seconded by Dr Blake, it was moved that it be the sense of this meeting that the Committee on Survey and Future Policy be not reappointed for the next year

DR PAULLIN "Mr President, I would not want to be placed, as the incoming President who has to appoint these committees, in the very embarrassing position of having to leave Dr Miller off the Committee and not reappoint a Committee on Survey and Future Policy If it is the sense of the Board of Regents that the Executive Committee can perform these functions, then I feel that that should be a function of that Committee As a matter of fact, I think we have an excessive number of committees in the College and their duties at times overlap, and I think that as soon as we can eliminate some of these committees, so many men serve on several of them while the College may not function better, there will be more time for meetings and for the transaction of business in the committees Of the three or four committees on which I have served one has had no report, the Executive Committee I am not at all sure but that the present duties of the Committee on Survey and Future Policy

belong to the Executive Committee of this College. I feel like Dr. Lee, that the Committee on Survey and Future Policy is a problem which directly concerns the Executive Committee. And then, too, the Committee on Medical Preparedness—there is no more necessity for that, and I think these committees could be merged into one, and then you would have plenty of time to transact business and not have to run from one committee to another. I am in favor of Dr. Piersol's motion, without prejudice to any one who is on the Committee."

Dr. Piersol revised his resolution to read,

RESOLVED, that it be the sense of this meeting that the Committee on Survey and Future Policy be not reappointed for the next year, and that its functions and duties be definitely assigned to the Executive Committee.

The addition was accepted by Dr. Blake, the seconder, put to a vote and carried, with one dissenting vote.

President Lee asked if any one had any matter that he wished to present for consideration.

SECRETARY LOVLLAND: "Our Board of Regents has been requested to examine a medical motion picture, with the thought that the College might engage in a further function of examining and approving medical motion pictures in the field of Internal Medicine. This particular motion picture was entitled 'The Principle of Allergy,' and was submitted by one of our Fellows. It has been examined by a few of our Regents. It was considered to be somewhat of elementary nature and to disclose nothing that the Board of Regents would be interested in approving or disapproving."

On motion by Dr. Stroud, seconded by Dr. Fitz and regularly carried, it was

RESOLVED, that the Board of Regents are not ready to commit themselves to any action whatsoever, inasmuch as it has not heretofore engaged in this activity and has not yet been impressed with the need.

President Lee declared the meeting adjourned at 3:30 p.m.

Attest E. R. LOVLLAND,
Executive Secretary

ST. PAUL *

SOME OF ITS EDUCATIONAL, CIVIC AND RELIGIOUS INSTITUTIONS

Nestled in a curve of the majestic Mississippi, the City of St Paul, one of Minnesota's oldest, takes pride in her pioneer heritage and in her steady growth since the roaring days of the covered wagon and Indian massacres

Now a quiet, dignified city—Capital of the great State of Minnesota—St Paul has one of the most corrupt-free governments in the Nation



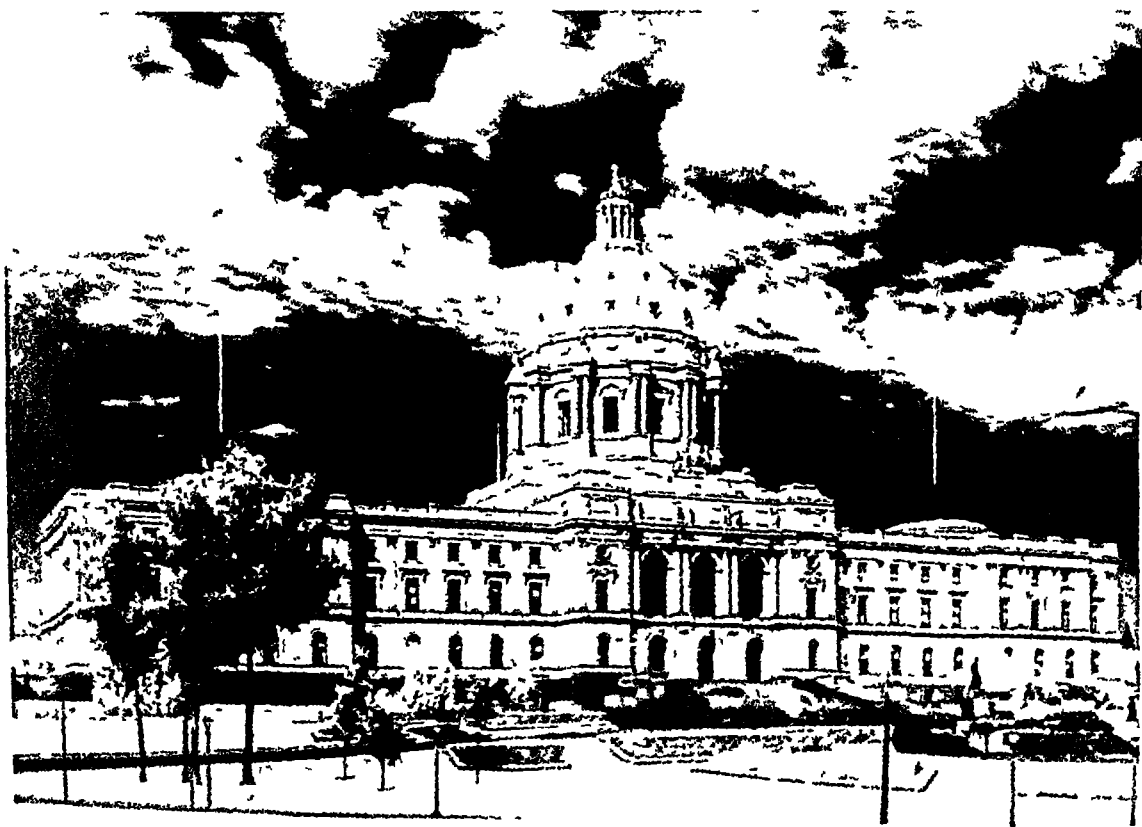
1—Saint Paul's Cathedral

* The Twenty-sixth Annual Session of the American College of Physicians will be held in St Paul, April 20-24, 1942

Crime has been reduced to a minimum under a commission form of government, the city's financial position has been brought into healthy balance, and a new wave of prosperity has been engendered by the nation's re-armament program

Railroading and wholesale houses, together with a considerable manufacturing business, make up the bulk of the city's economy. St. Paul also is a trucking center of importance.

With a population approaching the 300,000 mark, St. Paul and surrounding areas support four colleges and one university within the city.



2—Minnesota State Capitol, Saint Paul

limits. The city is the headquarters of the Roman Catholic Archdiocese of Minnesota and the Cathedral,¹ rising high over the skyline, is one of the largest churches on the North American continent. More than 300 feet high, it seats 4,000 worshippers.

Also looming large on the St. Paul horizon is the Minnesota State Capitol,² of the Roman Classic type, built of Georgia marble and designed by the eminent architect, Cass Gilbert. Completed and furnished at a cost of \$4,500,000, the huge domed building is considered an outstanding example of its architectural type.

Those who are familiar with the tomb of Napoleon in the Church of the Invalides in Paris cannot fail to see a resemblance in the setting of the

rotunda, with the second floor's circular corridors and balustrades looking down on the main floor

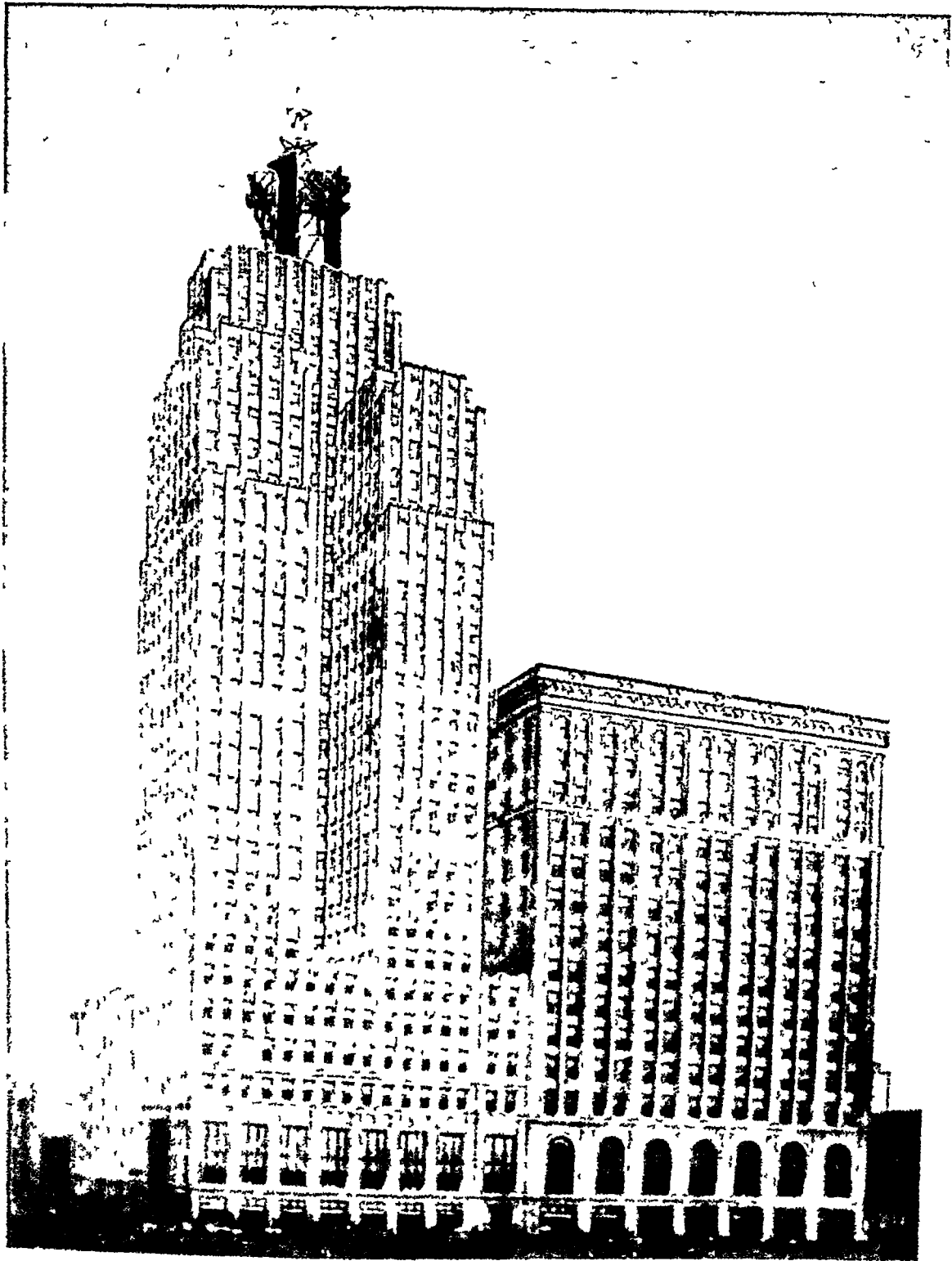
Newest, and perhaps most striking government building in St Paul, is the City Hall-Court House,³ an imposing structure situated on the bank of the Mississippi River and blending well with the city's modern skyline



3—Saint Paul City Hall and Court House

The building consists of an 18-story tower, surrounded by three stepped-back stories which spread out over the entire city block which the building occupies

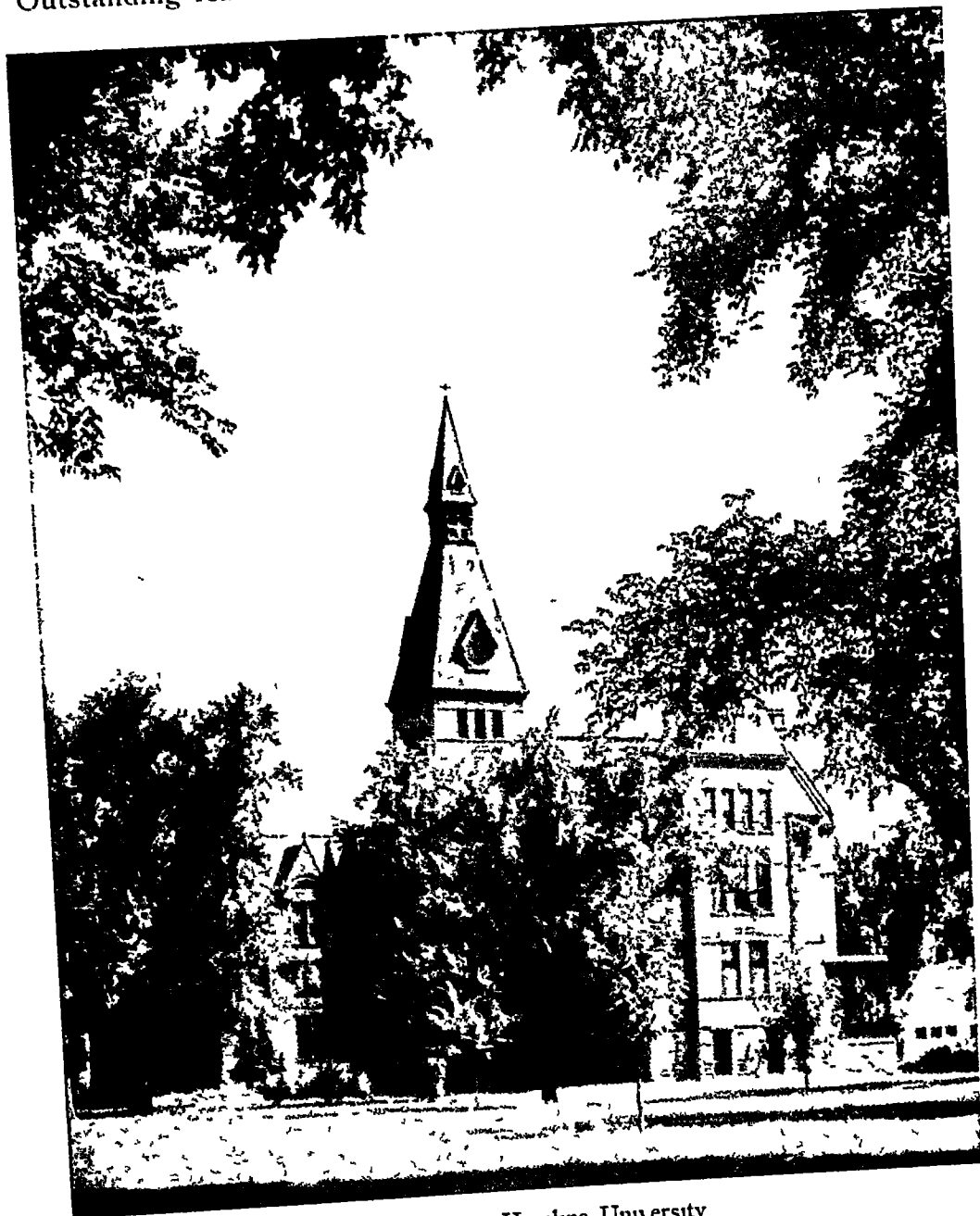
Not only is the City Hall-Court House a structure of dignity and beauty, it is the architect's dream of functional design, having within its



4—The First National Bank of Saint Paul

walls more than 80 per cent usable space as contrasted with the usual 40 per cent in most public buildings

Outstanding feature of the building is the huge onyx Indian, standing



5—Old Main, Hamline University

three stories high, symbolizing the God of Peace, holding a pipe in one hand and with the other extended in a gesture of friendliness. Dedicated to American war veterans, the statue is symbolic of the thought that out of conference and understanding comes the hope of peace in the world.

The First National Bank building⁴ is the first visible landmark of St Paul, whether you approach the city by train, highway or airplane. Its 32-story tower structure, standing clear and white by day, marked by a huge illuminated "1st" sign by night, is the city's tallest. The building is 402 feet high, with an added 100 feet of sign structure on its pinnacle.

St Paul's only university, Hamline,⁵ is situated in what is known locally as the "Midway District." Chartered in 1854, Hamline's first building stood in a wheat field by itself. Now the Hamline community is filled with lovely homes and the University itself is a cluster of buildings on a beautiful campus. There are nine in all, grouped around "Old Main."

The Library and Norton Field House are on Snelling Avenue, with Science Hall and the Union near-by. Hamline church is a part of the



6—Kirk Hall, Dormitory for Men, Macalester College

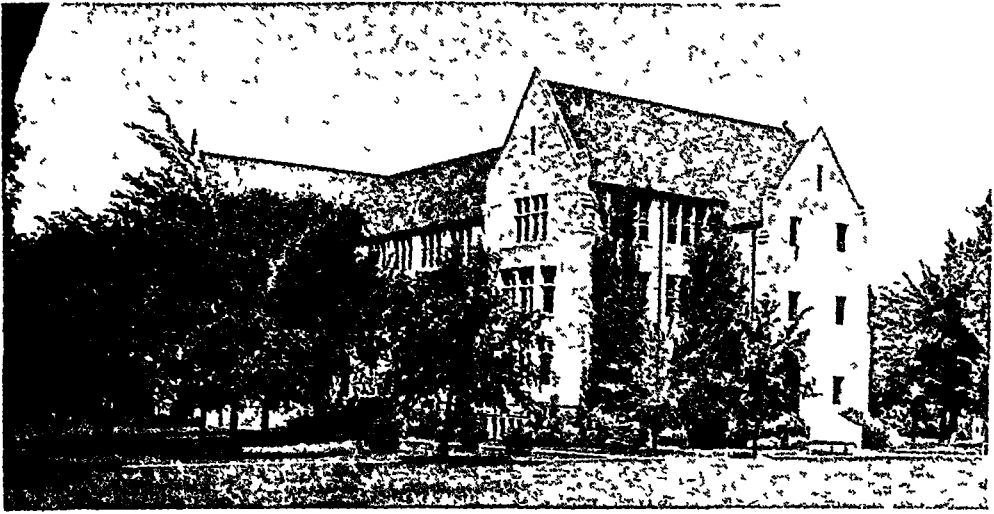
architectural scheme and is used for chapels, concerts, and religious activities. The Manor House is a residence for women and Goheen Hall, a residence for men, while adjacent to the campus is the home of the university president and seven other residences used by fraternities, co-operatives and homes for women. The athletic field and tennis courts are within a block of the campus. Improvements to laboratories were made last year and new equipment added to make Hamline a thoroughly up-to-date university.

Pre-medical and law and preengineering are among the courses provided at Hamline. The music department is unusual and annually attracts large numbers of students. The a cappella choir of 60 voices is outstanding.

"Macalester College," located a mile and a half south on Snelling Avenue from Hamline, was founded in 1885 by Dr. Edwin Dufield Neill, pioneer

Presbyterian minister and educator. Christian in purpose, non-sectarian in instruction and attitude, Macalester provides courses culminating in Bachelor of Arts degrees.

The College of St. Thomas,⁷ founded in the same year as Macalester, was the inspiration of the late great Archbishop Ireland. Originally in two departments, classical and theological, the College was divided when the late James J. Hill gave the archdiocese funds with which to establish the St. Paul Seminary. St. Thomas offers a four-year curriculum in which the first two years are devoted to general education on the college level and the last two years to the field of concentration, thus preparing students for graduate study in English, foreign languages, biology, chemistry, mathematics, history, social sciences, economics, business administration, philosophy or education.



7—College of St. Thomas, Main Building

In addition to the College of St. Thomas, the institution also houses the St. Thomas Military Academy, whose aim is "the highest excellence in the training of young men." It enjoys the highest ranking given by the War Department, belonging to the coveted "MS" division.

What St. Thomas College is in the field of men's education, St. Catherine's College⁸ is in the women's field. The College of St. Catherine, named for the Roman Catholic church's philosopher saint, Catherine of Alexandria, was founded in 1911 by the Sisters of St. Joseph of Carondelet. Since its establishment, the College has occupied a leading position in the educational development of the Northwest.

Concordia College, St. Paul's smallest, is a branch of Concordia of Moorhead, situated on the Red River of the North, some 250 miles west and slightly north of the Twin Cities. A Lutheran institution, it offers four-year Bachelor of Arts degrees.

In the field of sports, St Paul and its Twin City, Minneapolis, offer a wide variety of entertainment, both in spectator and active sport. Eleven golf courses are within easy reach of downtown St Paul—Town and Country, one of the finest in the nation, Somerset, University, Midland Hills, Hillcrest and Southview, all conveniently located only a short distance out-



8—Mendel Hall, The College of St. Catherine, Saint Paul, Minnesota
(Science Building)

side the city limits, White Bear on the lake of the same name, Keller—a county-owned course, and Highland, Como, and Phalen—all city-owned clubs inside the city limits.

St Paul is a member of the American Association of Baseball Clubs, and for those who enjoy fishing there are many fine lakes within a few miles of the loop district, and more than 10,000 in all of Minnesota—"land of the sky-blue water."

ANNALS OF INTERNAL MEDICINE

VOLUME 16

APRIL, 1942

NUMBER 4

THE EMOTIONAL COMPONENT OF THE ULCER SUSCEPTIBLE CONSTITUTION *

By GEORGE DRAPER, M D , *New York, N Y*

THE concept of the human constitution in relation to disease held in this clinic has sought to envisage the individual human being as an organismal entity built of multiple components. The latter have been grouped in the four categories of morphology, physiology, immunity and psychology, and the qualities representing each panel have been studied by whatever dependable methods were available. So far as subjects of gastric and duodenal ulcer are concerned, anthropometric technics ¹ have supported the earlier clinical belief that sufferers from that ailment belonged, within variable limits, to the linear division of mankind. Moreover, in the physiological panel of such persons the electrocardiogram has shown a consistent tendency to a long normal P R interval, a finding which accords with the widely held notion of vagus nerve relationship to ulcer ².

The present report presents an inquiry into the character of the ulcer type's psychological panel. It is not an attempt to prove again that such persons are especially sensitive to emotional stimuli. The fact that they are nervous and possess the habit of worrying has long been fully recognized. The purpose here is rather to investigate the emotional quality of the ulcer susceptible male, to correlate it as far as possible with his morphology and physiology and to form some estimate of its quantitative participation in the total reactions of that type of human organism. The ulcer itself may then be regarded as the inevitable product when these specialized human creatures react with certain peculiar onslaughts of environment, as well as with life generally.

Our experience among these interesting people over a period of 20 years or more leads us to believe that in the morphological phase perhaps they do

* Received for publication November 21, 1941

This work was done under a grant from the Rockefeller Foundation

The author is greatly indebted to Dr. Dana W. Atchley, Dr. John L. Caughey, Jr., and Dr. C. Wesley Dupertius for many helpful suggestions

Copyright, 1942, by The American College of Physicians

not all represent extreme linearity. But even in the stockier forms a definite tendency to gracile bony structure, narrow subcostal and obtuse gonial angles and long narrow teeth preponderates. The linear trend is also seen in their more delicately drawn, longer, narrower faces. There is also found a well defined emphasis upon the feminine component of that curious mixture of masculine and feminine qualities which is common to all human beings of either sex. This phenomenon is known as the mosaic of androgyny. Among ulcer bearers, however, this feminine aspect is not so marked as it is in males who develop gall-bladder disease. As will be seen later, however, the emotional response of the individual to conscious or unconscious awareness of this feminine component (which may be expressed with varying degrees of intensity in any one or more of the four panels of personality, i.e. morphology, physiology, immunity, and psyche) is far greater in ulcer bearers than in subjects with ailing gall-bladders.

In the physiological phase, perhaps the chief insignia of the ulcer patient are found in evidence of autonomic irritability such, for example, as easily sweating palms, tendency to widened palpebral fissure, slight sinus arrhythmia and prompt slowing of heart rate by deep breath holding or pressure over the carotid sinus. It is noteworthy that on admission to the ward most ulcer patients display an average or elevated pulse rate, but after a day or so this falls to a slower than average basic count.

A large majority of our cases have had good to superior intellects. Many possess a keen sense of humor, and their emotional responsiveness is swift and intense. They are often conscientious to the extreme, high principled and are forever striving to attain some goal notwithstanding difficulties which most men would regard as insurmountable. There is never a dull moment in the course of their disease, in their conduct of life and in their conversation. For this reason they are by far the most dramatic personalities on the medical and surgical wards.

Our problem then is to explore the thesis that in a specific type of human being ulcer production is the expression of the total organism's faulty life adjustment, and that this failure rests upon certain inherited and conditioned distortions of psychobiological energies.

The material is drawn from 80 unselected cases of peptic ulcer, both gastric and duodenal. In addition to the routine history which appeared on the hospital chart, each patient was interviewed privately for from two to five hours. These conferences were not devoted to a review of symptoms and diets, but to an effort to study the nature of the man within the patient, his reactions to events, and his attitude and feelings in respect to himself, his family, friends, occupation and life generally. All of these intimate records sound an astonishingly similar theme, but because of their large number and length only a few representative examples are presented here. It may be fairly said, however, that the psychological panel patterns are quite as characteristic for the ulcer potential type as are those of the morphology and function.

As has often been described in the past, it is possible, in many instances, to show that a severe financial loss, business reversal, personal frustration, sexual "sin," or a violent argument has preceded by one to ten days the onset of pain, hemorrhage, or perforation. Such concatenations of events cannot be presented mathematically as proof, but their empiric significance should not be thrown out of court for that reason. Moreover, in the lives of ulcer patients there are many instances in which distressing outward episodes are not followed by any gastrointestinal symptoms at all. Beyond these contingencies, also, there are numerous instances in which obvious external annoyances are of such trivial nature that they can hardly be credited with having precipitated the attack. Then there are the perplexing situations in which severe peptic symptoms strike unexpectedly when outer life appears to be serene. It must be remembered, however, that in the usual process of history taking we are accustomed to discuss chiefly that aspect of his life which is clearly defined in the patient's conscious awareness and recollection. That, after all, is the only phase of his existence which for him can be, there is no other. Yet from earliest times it has been known that there does exist an entirely separate current of psychic activity which, like a deep subterranean river, flows continuously and with mighty force beneath the superficialities of rational or waking consciousness. This unseen psychobiological energy has ever expressed itself variously and vaguely in dreams, in the occasional paradoxical conduct of intelligent men and in hysterical and neurotic states. In the past the exploration of this inner consciousness of man has been undertaken by many of the greatest medical philosophers beginning with Hippocrates and ending with the contemporaneous systems of Schopenhauer, Nietzsche, Freud, Jung, Adolf Meyer and their followers. For our purpose, however, it is sufficient to accept the existence of this deep emotional current without further discussion and to show that from it, in the case of the constitutionally susceptible person, there may arise traumatic stimuli of the same or greater magnitude and specificity than those from the outer or palpable world. For this reason dream material has been recorded in a few instances. This has not been done, however, for psychoanalytical purposes, but rather as objective evidence that the dream may contain pain-stimulating energy (see J. M., case 24). Throughout the biographical data there is evidence bearing upon the special nature of certain psychic traumata which befall mankind, and also upon the quality of response which so significantly marks the psychological panel of these equally special individuals who are alone able to develop peptic ulcer.

CASE REPORTS

Case 1 E. P. A., aged 37, hemorrhage January 6, 1937. This man, an Irish Catholic, is a heavy acromegaloid type. His body shows soft, rounded curves, denoting a strong gynec influence.

His father died when he was 10. His mother is living at 85, in Ireland.

The patient is the youngest of 6 siblings. A married sister lives in rooms

directly above those occupied by the patient and his family. The patient says that his father, a policeman, was a mild mannered man who was never cross nor lifted a finger against the children. Of his mother he says, "My mother did the spanking, she was a huskie. I was a wild youngster—I'll admit I was a devil." He likes his sisters—"one of them still buys all my clothes for me." She has no children.

At the age of 15½ the patient came to the United States (1915) in war time. There was a storm and an attempted firing of the ship by a German passenger. His first job was on the subway, and he tells in great detail (22 years later) all about two men who had been killed doing the same work he did. He said that these experiences did not disturb him. In 1922 he joined a cable gang of the New York Telephone and Telegraph Company and held that job 11 years.

He had been married at 25, on Thanksgiving Day (1925), to a girl 7 years younger. She was red-haired, positive and energetic, like his mother. Their first child, born March 1927, died in a few hours. When asked how the event affected him, he replied, "I felt sorry for her—she got so run down," and "It gave me a spasm of grief, seem' the little mite laying there." The second child, a girl, was born July 1928. "On account of the first experience I was shaky 'til I heard the baby squawk." The third child, also a girl, was born November 1930, when the older one was 1 year and 7 months. The patient had no symptoms at this birth.

Between October 1931 and the winter of 1933 he had two serious accidents, the "flu," and a mastoid operation. The children were respectively two and one and a fourth years old during these events, and he remarked that his wife was very busy taking care of them. Besides this threat to his own security occasioned by the deflection of her attention, he was laid off his cable job without warning soon after he left the hospital following the mastoid operation. At this point, because his savings were exhausted, and with great injury to his pride, he went on Home Relief. His wife got a job, but although her earnings helped, a new fear arose within him that if the Home Relief bureau should discover her action he would be in a bad fix. He lived in this state of fear of discovery from May 1932 to October when he got work on W.P.A. His wife, however, continued her "double timing" so that his fears in respect to the work situation continued. In the midst of this state of affairs his wife became pregnant for the fourth time. He said that when she found out she was pregnant "she raised holy hell and said to me, 'You damned clown, why didn't you know enough not to get me this way!'" He was frightened and humiliated by his wife's violent onslaught and felt the way he used to when his mother spanked him.

His first gastric symptoms started in September 1933, a month after this episode. In addition to his abdominal pains, he had severe cramps and fits of diarrhea (spastic colon?). For the next three years the patient had stomach distress off and on, and on April 26, 1936 he came to Presbyterian Hospital for operation. A normal appendix was found and surgeons reported feeling the crater of a duodenal ulcer. Due to coughing post-operatively his stitches burst and the patient now has an abdominal hernia. The constant bickering with his wife over the unwanted pregnancy went on in the months following his appendectomy. He continued an active sex life, however, notwithstanding his wife's frigidity, but always with an increasing fear of impregnating her. He used contraceptive measures against the Church's orders and "when I confessed the priest gave me holy hell." These conditions persisted until the present attack which started following his Thanksgiving Day wedding anniversary celebration when he consumed considerable alcohol and food. He vomited blood and the stools were black, there was no pain but a sense of fullness.

Discussion. Thus there appears the picture of the youngest son raising the devil from early boyhood, perhaps in protest over his mother's greater affection for his older brother. "He was hung pin in her eyes," he said. He

adventures to a strange land, and the arrivals of his children are paralleled by his series of accidents and illnesses. Financial insecurity develops, his sister-mother helps, and there is overstriving in the erotic field. He is condemned by his wife for getting her pregnant, and by his priest for not. Financial security and pride further threatened by fear of wife's "double-timing" while he works on W P A. Every phase of his life relationships is fraught with fear.

no

Case 3 T C, aged 38, pain, hemorrhage. This soft, nearly beardless, rather sinuoidal-looking man of 38 lost his father when he was 2 years old. An only child, he was entirely supported by his mother who worked her fingers off for him until he was 14 years old. "My mother," he said, "was the truest in the world, very solicitous of me and gave me everything." He admitted being completely absorbed in her "for she was a swell mother to me." He remarked that he had a fine relationship with his employers who, he says, "think well of me."

When he was 20 he married a girl who was one year older than himself. His mother was still living at the time, but he and his wife moved away to their new home. Yet although he moved physically-speaking, a later statement clearly indicates that his unconscious ties, especially in respect to his food, remained very strong. He proudly continued, "I'm still with the same woman. She runs everything, I just turn my salary over to her, and that's all I have to think of." His family consists of two boys and two girls, ranging in age from 16 years to 3½, and he says that he had no symptoms during any of his wife's pregnancies and labors. The arrival of the first child he took without any special emotional reaction, "but," he added, "they're (the children) more affectionate when smaller, they get their own ideas as they grow up and go to school." His sex relations with his wife have never been very active. "I'm not greedy for it. In fact, I'd not miss it if it never happened." This attitude is somewhat paradoxical when compared with his appalling self-confidence and cocksure talk.

He came to this country one year after his mother's death when his third child was one month old. Before he left Scotland he had noticed some indigestion. In commenting on this he said, apparently forgetting that after his marriage his wife had done the cooking for him, "but certainly those attacks must have been after my mother died because she always prepared my food specially for me, and I could always eat." He was successful in securing a job at once on his arrival in America—"No trouble at all," he said with utmost assurance. "Anyone can get a job if he wants. I'd dishwash if I had to, rather than be dependent on anyone." Thus he jumped unhesitatingly from a Scottish coalminer's job in his homeland to that of a grocery clerk in New York and settled his family easily, admitting that his wife was the boss. "She manages the children, but I hold the discipline over them," said he, with a knowing wink, "when she asks me."

In this country he had no indigestion until January 1933, 4 years ago, shortly after the birth of his fourth child. During the succeeding years he has had occasional spells of dyspepsia although no striking emotional upheavals occurred, but it may be mentioned that he has been earning \$35 a week for the support of his family of six. "It entailed some sacrifices to live on it," he said. "We couldn't go to the movies, but I don't bother about the movies anyway." The present attack started three weeks ago with pain and tarry stools. Two or three evenings before the hemorrhage the patient, as chairman of Church building committee, had been carrying on a fight to raise money for a scheme he had evolved for new church work. There was great resistance to his plan. The opposition group criticised him sharply. Though the plan finally went through he was unable to work in its operation because

of the bleeding episode "I'd have felt much worse if I had failed. But I had no thought of that. But," he continued, with a proud smile, "I've had no pain or bleeding since coming to the hospital." Here, at least, he finds a respite from "the sacrifices" which deeply humiliate him, and from the critical opposition in his church.

Just before the patient returned to the ward after our last conference he suddenly asked, without any connection with the topic under discussion, what I thought about the cause of divorce and all marital troubles. He had given much thought to the matter and was convinced that the unwillingness of both husband and wife to take responsibility, and above all the use of contraceptives were the main reasons. "Children have no mothers anymore," he continued, "because of divorce—and prospective children who are unborn because of contraceptives are denied the benefits of having parents." When I remarked that he had had no father he ever knew, he replied, "No, but I had a mother which made up for everything." From this he proceeded to tell how he never picked fights—"But if anyone laid a finger on me, I'd give him a good smack on the jaw. I'd be the first then." Apparently it had always been his ambition to be first in everything. "If any man beat me the first time my desire was always to beat him the second at whatever it might be."

Discussion This patient presents obvious eunuchoidal stigmata with strong feminine emphasis. The stimulus of the latter in raising his compensatory masculine bluster is clear. The maintained dependence on the mother and the ever-increasing threat to his male ego of the enlarging family is likewise apparent. The strange conceit of contraception as providing the threat of orphanage to unborn children again emphasizes his own intense dependence upon the mother.

Case 6 J. C., aged 38, pain, two hemorrhages. October 11, 1937. A pale, slender, earnest-looking young man whose father was killed by a truck when he was 19 years old. The mother is living and well at 76. She has a strong constitution and is still active.

His father, whose word was law in the home, had a dominating personality. The older brother (6 years older than the patient) ran away to Canada at 15. This left the patient as "oldest son" and much responsibility was given him. "I didn't know my dad as a man. He whipped us a lot." The patient feared him greatly and considered him to be hard and relentless. "He never praised us to our faces." His temper was terrible. Once when unhitching the wagon the patient forgot to take the trace off one whiffletree and the horse ran away and broke the pole. His father took a fragment of the broken pole and beat him. His mother intervened, as she often did, saying, "You'll break his leg." The father had no pets unless it was an older sister who was mentally handicapped. He was very tender to her. The others all got the same rough treatment.

His mother was a generous, patient soul whose first love was Dan, the oldest son. He came back after his Canadian flight, like the prodigal son. His mother regarded the patient with pity because he worked so hard; hence he welcomed the chance later to enlist in the army. It was evident that his father completely dominated his wife and all the children so that when he died, leaving her the farm, she and they were quite unable to manage it.

He says that there was not much rivalry between the brothers, and that he was especially attached to Dan, the oldest. "He was my hero brother and was killed in the war."

After his discharge from the army in 1919 the patient passed through a period of unemployment. He had fought six days with in France on the ra-

tionalized basis of fear of disease, but suddenly one night he saw the futility of his life and decided to go into the ministry "I got religion then and awoke the next morning with a great sense of peace and security" At the denominational college, where smoking was not allowed on the campus, he met two girls, one very good looking and one who would make a good minister's wife Though physically drawn to the former, he shunned her and cultivated the other's society

After four years at college he went to the Theological Seminary, having become engaged to the good looking girl after all At the end of a year in the Seminary he found himself exhausted and depressed because of financial restrictions, and especially because he was unable to compete socially with his classmates "I was pressed financially," he said, "and resentful that my friends could go to the opera and I could not" This situation led to violent conflict within himself as to whether or not he should appeal for assistance The struggle between his desire to keep up with the Joneses and the hesitation of his masculine pride to call upon his fiancée for help became acute, but he yielded and wrote to his fiancée who thereafter sent him \$10 a month

Shortly after this letter was sent he had a sharp attack of vomiting and diarrhea which was ascribed to appendicitis, but an operation disclosed a normal organ He was married a year later and during the ensuing three years he had gnawing pains off and on, especially during his wife's first pregnancy At this time also he was in controversy with two factions in his church and resigned His symptoms did not increase at the time of the child's birth, but he was disappointed that the baby was a girl After the resignation he was taken in by a friendly preacher so that he and his family were supported

In May 1936 he was in violent disagreement with the general assembly of his church in Syracuse to which his wife and 3-year old daughter accompanied him When he returned at the end of the month, he was greatly embarrassed at facing, on his first Sunday appearance, a highly critical and divided congregation "I felt I had been repudiated by the Mother Church" The patient also said that he had been upset all spring because his wife had had a miscarriage in January 1936, and that she was two months pregnant at the time of the Syracuse convention His first hemorrhage occurred on June 3

In connection with the above precipitating episode it should be reported at this point that the patient stated that his sex adjustment had never been satisfactory, and that because of *ejaculatio praecox* he had always practiced withdrawal as a contraceptive measure He was conscious of guilt in respect to any contraceptive plan because it "ran counter to nature's purpose" There was much residual guilt over early masturbation Superimposed upon this chronic fear and guilt there was now added the double blow—the Mother Church had failed to accept him and his wife was already deflecting a large share of her maternal energy from him to her three-year-old child and new embryo

The following November the patient was very busy getting ready for a church entertainment and picnic On November 25 he and his wife worked late at the preparations On the following morning his wife awoke feeling very ill and unable to continue helping him Although he knew she was pregnant he suddenly felt "lost, alone, and out on a limb" He then had a tarry stool

Discussion (1) On the farm the patient worked hard and got mother's sympathy and approbation as well as food, clothing and housing, i.e., working hard in a protectorate

(2) In theological seminary worked terribly hard, but he had scholarship, and his fiancée sent him money So again he had her sympathy and

approbation as well as food, clothing and housing (protectorate) The first vomiting and diarrhea came when the support was insufficient for both physical and ego needs. Fiancée's funds supplied the latter. Then he was better.

(3) When he took his first parish he was self-supporting and his wife was not working. This was his first experience at working hard outside of a protectorate. Although thrown out by his church he was taken in by a friendly preacher, and even though his wife was pregnant and the child became an added burden, he was adequately protected.

(4) Again at his second parish the patient was on his own. Having had his fingers burned once, he had the sword of Damocles hanging over him, lest he express philosophies which would result in his being dismissed. Thus he may not have been true to himself, and so a new set of wheels within wheels appeared for his conscience to digest. His hemorrhage followed the convention as he took up his preaching again, and faced a possible recurrence of his original dismissal.

(5) The second hemorrhage. The patient knew of his wife's pregnancy. All during the preparation to feed the crowd he consciously grew more and more resentful that she was pregnant and that he would have to carry the major onus of the exercises. Then when she was sick and "let him down" on Thanksgiving morning, a black stool appeared. Fear and resentment—she had forsaken him.

Case 9 J. F. D., aged 28, pain. The patient's father at 55 years of age is a hypochondriac, always taking medicine and displaying constant gestures of his hands. The mother at 50 has complained of stomach trouble for two years. She was seized two years ago with the idea that she was going to die. She told the patient's wife but not the patient. However, the wife told him two days after his admission to the hospital. "Mother has not had an easy time with Father," he said. "He runs around, out at night. It's because Father deceived her all these years that she suspects everyone." The patient left home twice because of her constant nagging. "My mother runs everything and completely dominates her family. She was always right, regardless of the facts."

The patient is the oldest of three boys. The youngest is six years younger than he, yet the patient does not remember his birth. At the age of 10 he first remembers his brother, whom he was forced to take care of like a nurse. He recalls only the fact that the baby brother was continually soiling himself, and the patient had to take him in and change him. The patient used to chastise the baby a great deal for this.

As the two brothers matured, the younger one got a good high school education and went to work in a life insurance company, advanced rapidly, married and took his wife home to live with his mother. The patient speaks smugly of the brother, "a good deal wiser." He is perfectly satisfied to live with Mother and lacks spirit to pull himself out and set up his own home, and anyway his wife has him right under her thumb.

The patient, on the other hand, joined the Coast Guard at the age of 18 years and after three years entered the merchant service, seeking adventure. (The patient says: "He had no reason to become a navigator, but he was continually looking for a chance to get out.") He was discharged, always looking for a chance to get out.

"Women have always been my downfall anyway," he said. He married in 1933, a girl whom he had known for a year. She had an excellent education, graduating with honors from high school, and had advanced to a good position in the same life insurance company as the patient's brother. The patient says of her, "She has a good head on her shoulders. She tried to put it over me at the start, not that she tried to boss me, but she resents my telling her what to do."

The first baby arrived nine months after their marriage, February 1934. The patient was then doing night work in a "speakeasy." The pay was good but the work was risky, involving the danger of arrest or hold-ups. The patient had been working at this job a year before he married and had led a very careless and wild life, drinking heavily, and although engaged to the girl, indulging in promiscuous venery. He was always greatly troubled with *ejaculatio praecox*. He had been faithful to his wife during the first years of marriage and says that his sex adjustment with her had been good. Although he and his wife are Catholics, he declared with slight braggadocio that he proposed to "disregard the rule against contraceptives."

The patient was informed by his wife of her pregnancy while dancing one night at a party. She said that it was only six weeks before her confinement. On hearing that he said, "I felt as though the world had dropped from under me. What would we do with all the bills we had? I certainly would have tough going, bread without butter, and coffee without cream. When I realized she meant it, I wanted to rush out of the place. It was just like someone telling you, 'We are going to take off your leg now,' and what would I do without a leg?" The news was too soon before the event, I wasn't eased into it—I wasn't prepared. It was a terrible blow. I got to arguing with her because I thought she had been holding out on me. I was angry and surprised—all in one."

During the four or five weeks before the baby came, the patient had pronounced stomach symptoms, and he began drinking milk instead of coffee. The stomach pains continued all through the year, with occasional periods of relief.

With the second pregnancy, as with the first, she delayed telling her husband until about two weeks before she went to the hospital for delivery. From the moment she told him he had gastric pains and lived on milk, crackers and cereal. "My mother told me," he said, "that my wife has an easy time, but that I have the pains."

About four months following the arrival of the last baby, the patient had a small hemorrhage which came on after an emotional upset at home. He said of this episode, "Lots of times I want my wife's company, and want her to fondle me, and often I want intercourse, but the babies would cry or need something, she would go to them and I would have to wait. In fact, I resented the babies—did not want them. When she would go to them I would feel the same as though a competitor took her away from me. I would want to kill him. As a matter of fact, I even threw books around the room. It burned me up inside. Then when I got out in the street I would realize what a darn fool I was, and that the baby needed her more than I did."

After leaving the hospital he drove a truck for a year and then entered the police department. He was a rookie for three months, then on patrol. In September 1937 he felt the strain of this work—later in 1937 he had return of pain. Had worked regularly in daytime until he went on force. Then irregular police life, night work, etc., nervous, irregular eating and sleeping. In 1938 he was put on a police boat and things went better with regular sleep and less dangerous type of police work. Following this respite, however, his appetite waned and pains increased especially at night. He resumed diet with benefit for three or four months. This he ascribed to further loss of sleep and trouble with his sergeant for breaking rules. He was upset at the thought of his captain's criticism.

In November 1939, he was driving his own car on a slippery pavement and

collided with a peddler. The latter was knocked down and the policeman on duty took his name. "So there I was a policeman myself, arrested for dangerous driving." That night stomach pains began and lasted for six to eight weeks. He had bad dreams that the Jew peddler died and that "they blamed me." This attack cleared up in three or four months and he remained well until something else happened. The next severe attack started in mid-January 1941 following a fight with his sergeant about not reporting on the hour. That attack continued until March 3 when it was immediately relieved on entering the hospital. His obstruction was operated on and he felt happy at the thought of an operation.

He has been well since the operation until he lost his temper with his wife two weeks ago and was conscious afterward of stomach pains and loss of appetite. He recognized that the coming and going of pains are clearly related to emotional tension and its relief.

Discussion One might summarize the mechanism of this man's emotional reactions in the following way. The patient began by being jealous of the younger brother whom he had mothered. This was intensified by the younger brother's prolonged control of the actual mother's concentrated attention. The patient exhibited an intense masculine protest in compensation for his inwardly sensed feminine component. Again, as in the former case, we see the desire to take milk and soft foods when the mother's attention goes to his "rival" children. So he remains a little boy, always frightened that someone will criticize or punish him and that the wife-mother will take her attention away to rival brothers.

The case further illustrates the obvious impossibility of obtaining any successful result by psychotherapy after irreversible tissue change has set in causing obstruction.

Case 14 J. G., aged 55. This Englishman came to America at the age of 21 and lived here alone until 20 years later. He is the second son in a sibling group of 11, seven of whom were brothers. The father's attitude to the patient was gentle and the latter did not fear him. The mother appears to have been a very lovable person, and the patient, with lowered eyelids, admits that he was her favorite and that he worshipped her. He was never a good mixer, was retiring, no scrapper, and had few friends. He always possessed a nervous stomach which responded adversely to personal criticism. Consequently, he has always tried to do right so as to avoid complaints. There is a marked emphasis on the feminine qualities in his make-up. As a little boy his habit was to hurry home from school and become, as he says, a nurse-maid for his mother, helping her take care of the many younger children. This experience he said led him into his present occupation of butler. He has never had difficulties with his employers and has always held his places for long periods of time. His mother's death when he was 40 upset him emotionally to such an extent that he imposed upon himself a year's mourning during which he eliminated all pleasures from his life. Whenever he heard music which his mother had liked he wept, and recalled that as a small boy music made him run and bury his head on his mother's knee.

His marriage, which occurred one year following his mother's death, has been childless although his wife did have one miscarriage. His wife and mother-in-law live together in an apartment while he stays with his employer. Thus his married life has consisted of home trips and early starts to make possible visits to his wife. For as long as he never dreamed his own home.

The patient had the unusual experience of two severe hemorrhages separated by a time interval of 25 years. In the fall of 1915 the patient, then in apparently good health, had just left a job when he received word that one of his brothers in the British Army had been killed at Nieuport in Belgium. The mother was also greatly depressed because she had not yet fully recovered from the death of her own husband, the patient's father, 18 months before. A few months later he found a new position as valet and steward on a house-boat. His employer was himself on a strict ulcer diet. On his first day he had an altercation with the captain about his duties. The point of issue was whether he should do crew's work or valet's. He refused the former, saying that he was employed as the valet and not as a sailor. The episode suddenly awakened him to the realization that he was doing, as he said, a woman's work and that he was either afraid or incompetent to do work which men did. Three days later his stomach pains began. Furthermore, all during this period he was disturbed by the fact that all six of his brothers were fighting in the British Army. He had many struggles with himself as to whether or not he, too, should join up. He turned his back on the issue, nevertheless writing one of his brothers advising him never, under any circumstances, to consider going into domestic service. On his return north in May 1916 he received a letter from his mother in England, stating that his youngest brother, who was under age, had run away from home to join the British Army. His mother took the boy out, but after a few weeks the lad again ran away and this time the mother did not interfere. The patient admitted he thought him very plucky, he censured himself for clinging to his security and felt the humiliation of the feminine tendency within himself. He also reported two dreams at that time which were quite clearly related to his early days at home when he assisted his mother in taking care of the children. Two weeks after the letter arrived he had his first severe hemorrhage.

During the intervening 24 years there were occasional little acid eructations but he worked adequately, was married, had small difficulties with finances in connection with the loss of a house which he had bought, etc. The present hemorrhage, which occurred on June 22, 1941, developed in the following setting:

His employer's family, on June 19, was about to move to Maine for the summer. The chauffeur, who was a fine mechanic as well, was not to go. The butler was told that he must drive the station wagon with the luggage and the other servants, who were all women, to the summer place. He resented doing the chauffeur's work just as he had that of the sailor and three days later entered the hospital with severe duodenal blood loss. The episode presents an analogy to the yachting experience of 24 years before. Both seem to have been precipitating factors. An emotional situation related to the present war was also involved. The patient says that on the conscious side he has been very little concerned about this war, but in a recent letter from his widowed sister-in-law, whose husband had been killed at Nieuport, he learned that her sons, now in their twenties, were fighting with the Australians in the Mediterranean. When the battle of Crete took place about June 1, he began to wonder and worry whether his nephews were with the Australian regiments which were known to be in Crete. This campaign occupied the early weeks of June and symbolically recapitulated the episode of the death of his brother in Nieuport 25 years ago. His anxiety and self-criticism for not having joined up like a man mounted steadily until the precipitating episode and hemorrhage of June 19.

Summary The remarkable circumstance that two hemorrhages were separated by a period of 25 years. This individual presented a psychological conflict related to the androgynous mosaic. He was conditioned

by his mother and his occupation in such a way as to augment his strongly emphasized gynec factor. As the result of a small superficial episode (brass polishing on a yacht) a bitter realization of the difference between men's work and women's work brought to consciousness the basic male fear that he will fail when the crucial test arrives. The World War provided that challenge, and he failed. Twenty-five years later at a time when he resents the nature of his work and this resentment is consciously expressed by an attack upon the limitation of his personal freedom and the necessity of doing chauffeur's work (again a man's job), the war situation involving his male kin obtrudes itself with exactly the same challenge.

Case 16. L. G., aged 38, severe, repeated pain for years. The patient was originally the second of nine siblings, now the oldest of six. Father's attitude to the patient was kindly. The mother, on the other hand, was a severe disciplinarian and taught the boys to fight anyone who attempted to thwart them. She continually told the patient in childhood that she would "knock hell out of him" if he showed fear. Notwithstanding this ferocity on her part, the patient was her favorite and has still, at the age of 38, been unable to leave her household and set up his own establishment, either as a bachelor or married man. Furthermore, she never displayed the slightest physical demonstration of affection. The patient's next younger brother became a prizefighter, and when the patient was 17 and 18 he used to watch his brother fight. As he watched he became terrifically excited, broke out into heavy sweats, his heartbeat changing from rapid to very slow thumping and he would have turning sensations in his stomach. "It was just as though I was fighting my brother's opponent myself and wanting to knock him out." This was in 1920. In 1925-26 when he was 22 years old after six years of this vicarious pugilistic interest, he had his first stomach pain. At this time, too, he nearly married a girl with whom he had been carrying on a sexual relationship, but he suddenly retreated and started an affair with another girl. The second girl he described as revolting to him because of her excessive hair distribution. During this affair, which lasted eight months, his stomach was continually uncomfortable. Both these girls were energetic and aggressive, "as bad or worse than my mother."

During the first interview in which this history was obtained the patient was resistant, viewed the questioner with suspicion and nervously twitched about in bed, complaining of his pain. At one point he said, "I wonder if the Lord is punishing me for my sins." He remarked that he couldn't see what discussion of his intimate life history had to do with his ulcers. He was bitterly aggressive toward Dr. Blank who had explored him some years before and who had told him that he would never be well. Furthermore the patient resented the fact that Dr. Blank had been angry with him and disciplined him for not keeping the diet which the doctor had prescribed. Even today he continued with great excitement, "Dr. Blank hasn't taken two minutes of his precious time to come down and see me and say, 'Howdy, kid.' He knew I was here four days ago and hasn't been in yet." His attitude was very suggestive of a puffed girl. In this connection it was interesting to note that notwithstanding the tremendous dynamism in the psychic phase of the personality, with the powerful aggression, virile muscular gestures and the history of fighting, the patient's body contours were rounded and displayed a strongly gynec emphasis.

It is a matter of some interest to compare the two histories on routine hospital chart, especially the history of the patient's reactions to life.

Hospital history

April, 1930

Special history

Following a year or so of indefinite pains in the abdomen, sometimes in the upper part, sometimes in the right flank, patient entered hospital for an exploratory, the gall-bladder being under suspicion. The preceding disturbances had been satisfactorily related to dietary indiscretion. The patient was an enormous eater and frequently over-indulged in alcohol. At operation a normal gall-bladder was found, but there was a thickened area in the posterior surface of the pylorus which was taken to be an ulcer. No further surgery was done and the wound was closed.

The evidence for early stomach sensations has been presented in the foregoing personal history and the very definite stomach pains and indigestion which began in 1925 when the patient was 22-23 years old occurred over the period in which his emotional conflicts were at high tension in respect to romantic affairs and the problem of marriage.

It appears from the record that between the years 1930 and the present admission in 1941, the patient was in and out of the Out-Patient Department and the wards, there being in all five admissions to the latter. During these years such notes as these were found:

Hospital history

12-8-30 Medical treatment is unsuccessful in this case to date because he has not been living up to dietary advice. It is suggested that he be admitted to Medicine for straight Sippy diet.

12-11-30 Readmission for another try at Sippy diet. As he improved and had remained 5 days without pain the following note appeared: "It doesn't seem unfair to assume that his pains outside the hospital are probably due to indulging his own tastes."

1-1934 A series of notes, all emphasizing the patient's "lack of cooperation" in the matter of following his dietary instructions. 4-1-37 "Same old story. Seems to get along well as long as he sticks to diet, but 2 or 3 times a year has recurrence of pain." At this same time a roentgen-ray showed the presence of a prepyloric ulcer.

Special history

During this period from 1930 there is one letter from the patient to the Social Service Department making excuses for not coming to the Clinic because of business engagements and economic pressure. There is, besides, a reference on 8-24-35 to an operation which had just been performed on his father for supposed carcinoma of the prostate gland. The doctors had told the patient that the old man could not live more than 6 weeks and sent him home with that message. "The sudden shock of this," writes the patient, "left me in poor shape with plenty of pains, even though before this experience I had been well."

Paralleling the hospital notes of dietary indiscretion, the special history discloses the fact that frequently during the same period the patient was involved in violent altercations with members of his family. As the oldest son he considered himself the representative elect of his mother. Whenever any one of his siblings in his judgment misbehaved he gave them first a tongue lashing and often an actual beating. Thus, for example, within the year he had a tremendous argument with and delivered a tongue lashing to his sister-in-law for not controlling her husband (the patient's brother) for spending too much money on her. During the same year he actually knocked his brother out with his fists for gambling and losing so that the patient was forced to help him out financially. The patient evidently was violently criticising his sister-in-law for not doing what the patient's mother had done to him and his father. He also admitted that his fear of losing money was always present in his mind. All of these outbursts were followed regularly by increase in stomach pains. About 10 days before his last admission on April 13, 1941, the brother's store was destroyed by fire and the patient lost considerable money as a result. Four days after the conflagration the severe stomach pains which brought him to the hospital developed.

During his stay in the hospital several minor episodes of pain occurred, one or two of these at night. For example, he had pain immediately after lunch on April 18, 1941,

which he blamed on a boiled potato. Further questioning, however, brought out the fact that during luncheon he was reading the account of the episode of the Esposito brothers who, as the patient said, "attacked and killed their victims like mad dogs." He then continued, "I felt my stomach curl up inside as I read." On April 24, 1941, the patient woke at night with pain. He admitted, however, that he had awakened suddenly with stomach pain from a dream in which he was engaged in a terrific fight wherein he was attacking violently. It was interesting in this connection that for the three previous days the patient had been on a full ambulatory diet without any discomfort. He further recounts a pain which occurred in the middle of the night one month ago, immediately following being awakened by his mother who was feeling ill. He said that his first reaction toward his mother had been resentment at having his rest disturbed, and this morning, April 24, 1941, the nurse awakened him from a mid-morning doze. He resentfully asked her what it was all about and within a few minutes pain developed.

Discussion This patient displays admirably the ruthless bluster and violent aggression in conduct toward the outer world, but within, supported by his strongly feminine emphasis in both soma and psyche, he is like a girl child, unable to leave a dominating mother and striving to emulate her and retain the favorable protectorate in which she holds him.

Case 17. A. H., aged 32, indigestion, hemorrhage. March 23, 1940. This patient is a sturdy American of German descent. He entered the hospital for blood loss, with symptoms of dizziness and tarry stools. He had had gas pains for several months. His routine hospital history was typical of those given by peptic ulcer patients. Both his parents are living, they are Catholics, and the patient was strictly brought up in the Church. He was married 11 years ago at the age of 21 and has a daughter 10 years old. Four and a half years ago, in 1936, he was divorced. His wife soon remarried and his daughter was adopted by the second husband. He has been a rather heavy drinker.

Shortly after his divorce he began keeping company with a girl who was a few months older than he. The relationship developed into an actively sexual one during the latter half of 1937, 1938 and 1939, when it became, as he said, "more like a marriage." Indeed, he said he would have married except for the economic situation. This was the only reason he gave at first for not marrying, but later on he admitted that he feared the church's attitude. "They would excommunicate me if I remarried, and that would break my mother's heart," he added. In this connection it is of interest that once when quite drunk he started to enter his priest's house to ask the latter why he couldn't marry again. The priest sent him away and told him to come back when he was sober, but the patient never returned for the discussion.

This conflict obviously had been "burning him up" since the complete sexual relationship had been established in late 1937. His first indigestion occurred in December 1938 following difficulties with his employer whom he felt was treating him unfairly. The mild indigestion continued off and on until August 1939 when he had a violent altercation with his boss which led to the loss of his job in October. He was unable to get another job and returned to live with his parents. His fiancée was also leaving with her for a similar economic reason. From then until his hemorrhage in March 1940 the patient had recurring attacks of pain.

It had been a disappearance of all symptoms for a period of two weeks in the middle part of March, and the patient felt well and enthusiastic. He told his fiancée of this and suggested that they marry immediately. To his surprise and annoyance she refused, saying that she wouldn't marry until her parents were gone. "My father would be a good deal more than I should do the same." This conversation occurred

late on Saturday night and three and a half to four days later the patient had a hemorrhage. His companion had repudiated him in favor of her parents.

It was suggested to the patient that he seemed to be waiting for his parents to die in order to marry. "I'm waiting for no such thing," he snapped resentfully, on the defense. "I'm having fun trying to keep my father younger."

A dilemma confronts the patient. If he marries he faces excommunication and so breaks his mother's heart, or he continues to live in sin and so is oppressed by guilt and fear of punishment. His economic security is dubious and his girl in the end forsakes him.

Case 23 G McP, aged 41, perforation July 29, 1940. This man, showing strong gynec emphasis in both morphological and psychological panels, had been a fine soldier in the great war. He went over the top many times with fear in his heart, but showing perfect action courage. He was moderately gassed and wounded in the knee. After the war, at the age of 20, he came to Canada with his parents and sisters. Six years later his father left and returned to Ireland with his oldest sister. Then, after living for eight years with his mother and two sisters, he tried living by himself, but at the end of two years he returned to his sisters who were then both married.

During the following years, 1926-36, the patient said, "I was always looking for excitement, women and liquor." He tried giving lessons in motorcar driving and also worked himself as a taxi driver, but, said he, "I couldn't stand it. The strain of avoiding accidents gave me pain in my stomach every two or three days." Then he moved to Chicago and New York during 1935 and 1936, still driving taxi and teaching, and still having pain. Finally in 1936 he began living with the woman he was subsequently to marry. She was a divorced and childless woman who was four years his senior. He had not been altogether faithful to her during the period of their relationship and subsequently was very active and promiscuous sexually, but he always feared she would discover his "bad behavior." During the 18-month period just mentioned, the patient plied his newly acquired trade of hairdresser and found it meticulous and responsible work. He continually feared he would not do a satisfactory job or might burn his client. It made him feel tense and nervous. In 1937, while still living with his mistress, he started a clandestine love affair with another woman. He lived in constant fear of discovery. One afternoon in February of that year he met his second paramour at a New York hotel and began drinking at once. "I was very nervous and apprehensive." Between five and seven o'clock he had two sexual encounters and at two a.m. his ulcer perforated.

An emergency operation saved his life and during his recovery his first companion decided to take him back and "take care of me." Three months after the operation they were married. The marriage was a purely maternal affair and conjugal relations were never reestablished. The patient's stomach symptoms were almost negligible for about a year and his general health good. At this point he resumed clandestine love affairs and almost at once his pains began again. He recognized their relationship to his fear of discovery.

Discussion The patient said that he had always tried to please everyone lest he lose friends and that the same thing applied to his sisters and mother. He knew he had been excessive in sexual matters and had sought adventure and violent activity far too much. These trends seem to point to compensatory efforts in view of his marked effeminate appearance and manner and the choice of his final occupation.

Case 24 J M, aged 25, pain, multiple bleedings. This gentle, girl-like youth was the youngest of four siblings. He was 17 when his mother, to whom he was inordinately attached, died suddenly of heart disease. In speaking of her he said,

"Anything you wanted, you'd get" It was rumored that an older brother, Francis, was her favorite, but the patient quickly added that she herself had denied that. After his mother's death his father tried to take her place with the children. "He can't do enough for us, prepares our breakfast, and has spent \$2000 on my stomach in the past three years and I've never heard him mention it." Both the older brothers are huskier than the patient, but both have "weak stomachs." One of them probably has an ulcer.

In speaking further of himself he said, "My brothers treat me like a 3-year old. Whatever I did was always wrong. If I bought a suit or hat or ties, no one liked them." He was never abused physically and was always the baby. The brothers are pretty strong. One, Francis (ulcer), is of the patient's height, weighs 185 (pt 145 highest). Thomas is 6 feet and weighs 200, he is a physical instructor and a fine athlete. The patient played baseball, but in the past two years has felt himself going backwards, slipping, perhaps "growing old." He recalls that he always had a poor appetite at table and picked at his food. His brothers would say, "How do you ever expect to get big and strong like us?"

He is a sensitive, mild lad, with a rather dreamy look and not much physical energy. There are swift little facial twitches and a habit of swallowing often. He always has noticed his hands, which he thinks are small in comparison with those of other boys of his age, yet he could do as well with them. He never went in for scrap-ping but could hold his own if molested. He knows he has small bones but has no sense of genital inferiority.

"Since my brother had an ulcer and he is older than I, and the oldest boy, and Tom also has a weakish stomach, I feel that I should have a worse stomach than any I'm more nervous and frighten easier."

Episodes of pain or bleeding

1933—Loss of mother. First, after mother died. "At Mother's death I was very grieved and had an all gone feeling" for three months. "It never went away completely. A year later I consulted a doctor for it. I kept telling myself that I was old enough to take care of myself, but yet inside I knew I couldn't. You see, I was so much younger (eight yrs.) that I was very close to her, and felt that my father was very distant. I never knew him until lately."

1935—Aggression and insecurity. Second, pain, then operation. His first job after leaving school at 17 had been at a soda fountain. A colored customer threw an ice cream cone at him which he threw back, hitting her. He left in a great temper and had stomach pains all through the day and all night. Then he got a job as a porter. It was hard work and boring, irritating trying to get his loads through the door. Increasing pains led to operation, 1935. Even though he hadn't liked the job he tried to get it again after the operation because he had a driving eagerness to work.

1937—Sex guilt and fear of failure. Third, bleeding. At the time the patient was having occasional sexual intercourse with a friend. This became an established habit. But he admitted it was always associated with guilt, fear, and solicitude for the girl. At the same time he had been put on a job in a linen house where his father's sister, who was also his first cousin, worked. She nearly drove him mad by giving him a lot of work problems to solve, real mental work. The patient always thought that her servant did it as well as it should be done.

1938—Sexual intercourse with mother. Fourth, he paid attention to pain and bleeding. He had sexual intercourse with his mother for the first time on January 1, 1938, six months after the operation. He was determined that his stomach was worse after the operation. He was not at all satisfied with the results of the operation. So he

lost his second mother. For two weeks before admission he lived on crackers and milk and eggs. He imagined that his stomach was "full of ulcers."

Pain "this morning" One morning shortly after his admission to the hospital he reported having had a bad dream during the night. "I saw my girl on the roof with her mother. I fell, either off the roof or downstairs. I was frightened when I saw her mother and I backed up and stumbled in the get-a-way." The occupant of the next bed reported that while dreaming the patient had his hands pressing on his stomach and was moaning, but he didn't wake. The patient says, "Perhaps bringing the girl into our talk yesterday may have stimulated the dream." He thinks the girl's mother must know of their relationship, and he always feels awkward and guilty in her presence.

He often dreams of falling off great heights, and always feels squeamish and gasps with fright when looking down from high places. He thinks there was some talk of his having been dropped as an infant.

On returning home after his discharge from the hospital he had an irritating session with his family. His policeman brother drove him home, and on arrival he found his sister with friends. He was annoyed and sulked on the roof until they left. They were from the store where he and his foster sister work and he didn't want the relationship known. When they left he came down to find that no supper had been prepared for him. He was furious and in addition it made him late for a date with his girl. Pains followed in a couple of hours.

On some days he says he can't think and is confused. On those days his job goes badly, yet he feels and knows he can do far better. Being a Catholic, he went to Novenas to try to help himself, but he didn't attend regularly and then chided himself for his delinquency. This effort was of 1940 and during that year his stomach was never better—no pain. In June 1940, however, after he had ceased attending the Novenas, he had sudden bleeding, no pain, no warning. "It was just supernatural," he said. "I knew a few days before that I would bleed." He had become apprehensive about his bleeding attacks so that every time he went to stool he feared he would find blood and was greatly relieved when he saw "all clear." This fear accompanied every stool since leaving the French Hospital in May 1938, especially from June 1940 until now. In previous bleedings he had always a month or more of severe pain as a warning. Now he is terrified every morning that he will find blood.

It would appear that the patient's problem is concerned with fear arising from two sources: one, loss of maternal interest, and second, "sex is sin." Ranged before him are guilt of extra-marital sex relations, a commitment by his conscience to marry the girl whom he doesn't love and doesn't want to marry, and finally fear of losing the mother principle. He is therefore confronted daily, hourly, awake and in dreams, by the symbolic figure of a policeman who actually had frightened him when he was 7 or 8 years old. Consequently, fear of detection and punishment for anything he might do pursues him. Police, priests, and his primitive concept of a jealous and punitive God are merged in an ominous pall above him. In this predicament, hospital nurse and physician stand as the only mother surrogate.

During his last hospitalization he admitted that he had resumed his sex relations with the girl and that he was immediately conscious of a strong sense of sin, guilt, fear, and stomach pain. He said, "I know that marriage will save my soul, but I'm afraid to marry the girl when I don't love her." The situation presents the eternal conflict between man's desire for security and a natural sex life, and the fear of his organismal inability to achieve the first, or exercise the second without condign retribution.

Case 27 A P, aged 41, two perforations. The patient is a French Basque who lived with his parents until the death of his mother when he was 27 years old. He is a small, quick-moving, hot-tempered man. His first stomach pains appeared when he

was 25 and working as a baker. He had come to the United States with his parents two years before. At the time the pains started he had been gambling a great deal for over a year, much to the distress of his mother. Often he would lose his whole salary and be filled with guilt and fear because it hurt his mother so. "I suffered and felt it in my inside." By constant criticism his mother interfered with his feeling of his right to gamble. He knew it hurt her yet he kept on "falling from grace."

As a child he was always in conflict within himself over his fights. He couldn't stand criticism, interference, being "bawled out," or physically attacked. He defended himself if attacked, but became so violently angry that he was afraid to hit hard lest he kill. He thinks that his mother's continual interference with his gambling instinct and his resentment at her attitude caused his early pains.

The patient married a few months after his mother's death and changed from his former work to the fur industry. The first child was born two years later. He was happy during his wife's pregnancy, and had no nausea or conscious worries. He felt a healthy growing sense of responsibility and gambled less. Though he had been active sexually before marriage he remained faithful to his wife and felt no guilt or fear concerning his youthful experiences.

His fur business, however, did not turn out well so he changed again to the position of elevator boy in an apartment house. With his wife and his four-year old child now to support, he was afraid he might lose his job if he made any mistakes, "and running an elevator is a nervous job." About the middle of June 1933, the superintendent of the building asked him to make secret reports on the tenants. The patient refused and was upheld by the agent, but the superintendent kept nagging him to discipline the skylarking children who lived in the house. Finally one evening the superintendent called him a softie and bawled him out severely. The patient became enraged and just managed to control his strong impulse to smash him. That night he slept badly, ate no breakfast, and went to work at 8 a.m. on his elevator. At 9 a.m. he perforated.

After his recovery he became a waiter, which he says is a very aggravating business. "If the headwaiter doesn't like you he picks on you." It happened that for the ensuing five years he was in a position under constant irritation by the headwaiter, and his stomach was uncomfortable during that entire period. Toward the middle of February for the first time since his marriage the patient became involved in a sexual relationship with another woman. It so happened that by accident, while walking on Broadway with this new companion, he met his wife. He quickly elaborated a story to explain his situation, but that night was severely criticized by his wife, who he said, was evidently terribly hurt by the experience. He broke off his outside relationship abruptly and for the ensuing two months made every effort to reestablish his wife's confidence in him. About three weeks later he found that she was spying on him and this threw him into a violent anger. During the subsequent week he was never convinced that she had accepted his renewed fidelity, and felt that he was still under suspicion. Not only was he uncomfortable because he was being hurt, but he was exceedingly angry with her for not accepting his real effort to win. On the evening of May 5 he served a large wedding party dinner at the hotel where he worked. The evening was some crooked dealing by the dining room captain in regard to the patient's tip. The latter flew into a rage, accused the captain, and this led to his perforation. The next morning his second perforation occurred.

The patient's view of his life story by saying that his stomach was worse after his second perforation and that following his unfaithfulness to his wife he had the same pain as he had originally had about the hurt to his mother. He said that he was not sure if he would not have some more pain. "It is a very strange thing," he said, "to get a pain in the stomach when you are doing your best to be a good person."

This individual illustrates again the pattern of chronic guilt and fear and the precipitating episodes of violent outbursts of anger

GENERAL ANALYSIS OF ENTIRE GROUP

Because space does not permit printing all 80 records a summary of their content is offered. It should be noted, however, that the fear emotion arising from various stimulating mechanisms is the essential point. Furthermore let it be admitted that all human beings are subject to loss of maternal principle, to sex experience, and to causes for jealousy and aggression. The fear response to these stimuli within each individual, however, is an entirely personal matter, determined by his protoplasmic constitution and the nature of his childhood training and education. Moreover the degree of guilt and fear which is aroused in a young man by sexual experience, for example, is almost directly determined by the early teachings concerning it to which he has been exposed. In our series the quality of reaction to this particular problem seems to have been equally divided between fear and its absence.

TABLE I
Distribution of Chief Fear Sources as Elicited in the Group of 80 Cases *

	No	Per cent	No	Per cent
1 Inner sense of insecurity based on actual or supposed physical inferiority including gynec emphasis	63	84.0%	12	16.0%
2 Persistent hold on mother principle and fear of loss of mother surrogate's approval	76	97.4%	2	2.6%
3 Jealousy and aggression	50	64.9%	27	35.1%
4 Guilt and fear related to sex problems	31	49.2%	32	50.8%
5 Compensatory striving	41	56.2%	32	43.8%

* Out of the 80 cases a few failed to supply adequate information in one or another of the five categories. Hence the total number of cases varies in each.

DISCUSSION

Themes which emerge from the foregoing biographies are apparently related chiefly to the instinct of self-preservation. In the lower animal forms, at least so far as we know, this applies to bodily existence alone. In man, however, there stands in addition the supremely important consciousness of personal identity. For him this ego transcends all else, is defended to the last with his strongest effort, and its injury or destruction may be followed by tissue deterioration or death. Thus, while organismal reaction in the interest of survival is common to all living forms, and expressed as expediency dictates either in advance or retreat (fight or flight), man's conduct in these respects presents complex and often paradoxical patterns. Moreover the unpredictability of human behavior may be influenced by a person's estimate of his own capacities. Such judgment, however, may often be unfavorable because of the condition-tinted lenses which each man dons in early childhood and wears throughout life.

In the depths of inner consciousness, all human beings, especially males, depend for their sense of security primarily upon sound and powerful bodies—consequently there are in the main two somatic factors which may operate to undermine self-confidence. The reaction to these structural implications seems to be most intense in peptic ulcer subjects. First is the growing boy's recognition that he has a weak and puny frame, or that he is smaller than his brothers and pals. The second, in men of all ages, arises from the remarkable phenomenon of androgyny already mentioned. There is plenty of evidence for both of these biological inadequacies to be found in the foregoing biographies. Especially does it seem that unconscious awareness of the feminine component may be a stimulus to the over-exploitation of their virility which is so characteristic of ulcer bearers. Indeed it may be said that a man who possesses that degree of femaleness which threatens the authenticity of his essential maleness becomes subject to deep-rooted unwitting fears lest he fail to play successfully the masculine rôle in life. This may be called the basic male fear. In connection with it one may refer again to Cannon's⁴ original observation that it was the male cats which exhibited digestion-inhibiting effects perhaps owing to appropriately masculine resentment at being tied down on the operating board. The digestive movements of the female animals were not disturbed.

It may be said, further, that there are two phases of the survival problem which present themselves to man. One of these, his position in space, is a matter determined by the cooperation of bones, joints, spinal nervous system, striated muscle, conscious perception, discrimination, choice, and volition. Reactions in this phase are observed as outward conduct and determine his life of relation with the physical environment. The other aspect, that of the inner life of existence and procreation, is governed by the cooperating agencies of smooth muscle, uninfluenced by volition, the hypothalamic-autonomic system and the emotional reservoirs, whatever they may be. Consequently the whole vital mechanism reacts to fear stimuli from both outer and inner environment.

It is known that if the stimulus origin lies in the outer world the autonomic-smooth muscle-endocrine complex operates to prepare the creature for a vigorous coordinated physical response. This should normally terminate in the powerful, consciously directed conduct of fighting or running away. If the fear stimulus, however, should flow from the waking phantasy-world or the dream, confusion, indecision, and futile incoordination of the whole mechanism ensues. Under such circumstances there is no reality menace from which to flee or upon which to direct an attack. Nevertheless, notwithstanding the absence of an outer target, the defense mechanism has been emphatically provoked and the individual inwardly senses its psychophysiological distress.

Some experimentalists have shown that in the struggle to meet a given stimulus there are two phases: between the phase which controls outer conduct

and that which directs inner. Such conflicts rest upon the fact that man displays intense feeling states and greater physiological disturbance when the dangers menace his idealized ego rather than his body. In war, men go over the top with fear of wounds and death in their hearts, but still they send their bodies forward while the gastrointestinal tract runs away. It was well said by Henry of Navarre as he charged into battle "Body, you're trembling, but if you knew where I was about to take you, you would tremble indeed!" And that is the daily self-imposed task of the ulcer-bearing male.

In this connection the question has lately been raised in England^{5, 6, 7, 8} whether or not what seems to some observers to be an increase in peptic ulcer is due to stress of war. The figures from several sources are somewhat conflicting so that as yet no positive deductions can be drawn. However, it is now quite impossible to make comparisons between Army and civilian groups so far as exposure to danger is concerned. Moreover in two or three of our cases who went through frontal conditions in the last war, stomach symptoms were notably absent during the combat periods. Ulcers seem to reflect disturbance in the inner rather than the outer world.

It may be questioned, however, whether episodes which concern self-preservation in man are more disturbing than those involving his companion instinct of self-perpetuation. Indeed, the sex problem may, in the present stage of his evolution at least, hold greater dangers for him than the other. There can be no doubt that the energy of those psychobiological forces involved in reproduction is equal in man to that which exists in all animal forms. Consequently, whether for good or evil, the restraint upon it which customs of groping civilizations have required, gives rise to conflict within the consciousness of the individual. In a curious way this conflict of social law and biological necessity actually converts sex problems into fear problems. Any infringement of a taboo concerning the relationship of the sexes at once exposes the offender to his own or public criticism. The sufferings which flow from the patient's sense of guilt in these circumstances are no less terrible forms of punishment than those imposed arbitrarily upon the sex miscreant by a society still trembling under the Church's despotism of fear. And at that point the dial which indicates the source of disease producing emotional disturbance swings again to rest with its needle pointing out a menace, not to life perhaps, but to the important ego. Fear promptly surges through the individual and all the complicated mechanism for defense and attack is set in motion. To the end of total self-preservation, then, we can accept fear as the master emotion. In man it emerges with equal speed and intensity at threats from either the outer world of reality or that inner one which is composed of physiological and emotional forces. Laymen are more familiar with the latter under the name of conscience, "which makes cowards of us all."

It is difficult to review the records of individual reaction or reflex conduct of the digestive system which have been presented without recognizing that

emotional crises are correlated with stomach symptoms quite as clearly as are "dietary indiscretions." Indeed one is reminded of what every mother and pediatrician knows, that after an outburst of anger, or the experience of fright, infants and very young children may refuse food, vomit, or have diarrhea. In ulcer-bearing persons whose capacity for food reception is easily disturbed one sees again Nature's purpose of providing the infant with security at meal time. It is a simple thesis because deprivation of nutriment is the chief menace to the infant's life.

Instinctively, following the severance of the umbilical cord, the baby seeks the breast in his effort to reestablish the food line as promptly as possible. Consequently the focus of its urgent demand is directed upon the mother who actually is its only source of nourishment. During the next six or seven years as other and varied hazards to safety increase with awakening consciousness and the complications of ever widening environment and social relationship, the child still finds in the mother its surest guarantee of security against them. Thus, with the first gulp of maternal milk, there is formed a mutual life-saving and perpetuating relationship—the child's life and the mother's immortality through her offspring—which remains by force of habit almost indestructible throughout the lives of both. This relationship, however, appropriate and significant as it may be in the early months and years when the mother's ego perpetuation urge and the infant's very life jointly hang upon it, can easily become a destructive force for both at a later time when each is fully capable of negotiating life independently as nature demands. In the mother's case the evil effects are expressed in exacting homage and exerting selfish power control; in the case of the son or daughter, the infantile emotional structure, retarded and ensnared within the offspring's adult frame and intellect, obstructs vigorous and independent action of the whole organism. Thus crippled it moves through life beneath a pall of free floating apprehension afraid of its own shadow when glimpsed alone and unaccompanied by that of its protectress.

As far as the infant of a day or a month or even a year old, is concerned, his reliance upon the mother is quite impersonal. In his conditioned emotional patterns she represents only the means of survival, not a recognized personality. Later on the mother inevitably assumes an intensely personal and often demanding outward relationship from which the maternal significance as means of survival may disappear entirely. Indeed she may die or depend upon her offspring for support when they are still very young. Her often her ruthless control forms a menace to her children. In the unconscious level, however, she continues to stand as the symbol of her primary function. Therefore, the mother principle carries on throughout life, in the many guises. Table 2 shows a grouping of these possible symbolic representations.

When one reads the routine histories of many cases of gastric or duodenal ulcer one is struck with the repetition of the fact that the stomach is

sick and consequently has difficulty with strong foods. That basic thesis has determined the obvious existing therapy, namely, treat the sick stomach gently as you would the delicate digestive organ of the infant. It is also common experience that many cases have repeated hospital admissions and form a long line of "follow-ups" in the out-patient department. Almost without exception the records of these multiple visits repeat comment upon whether or not the patient has cooperated in carrying out his dietary regulations. Indeed the physician often sounds a note not unlike that of an irritated school ma'am whose recalcitrant pupil has failed to do his homework. When you read the intimate histories of persons who have ulcers, however, the impression develops that these individuals, like frightened neglected children, are striving continually to recapture and maintain the mother principle which had ministered so meticulously to the demands of that delicate infant receptacle for milk.

The more one observes these victims of chronic fear, often highly intelligent, futilely dynamic and over-striving people, the more one is forced to see

TABLE II

Mother Principle
or
Means of Survival

- I Own Mother —
- II Surrogates Foster mother, grandmother, wife, daughter, sister, nurse, doctor
- III Symbols Social group ("I belong")
 - Business firm, job
 - School, college (Alma Mater)
 - Church, brotherhoods, masons, etc
 - Inherited money, money in general
 - Food and housing
 - Hospital

in them supporting evidence for the notions concerning "Body Image" advanced by Schilder,⁹ Coghill,¹⁰ Bruch¹¹ and others. These authors concur in the belief that our bodies, indeed our whole personalities, have grown into images to ourselves of what we believe ourselves to be. "This image is built up in ourselves," writes Schilder, "in accordance with our instinctive attitudes," while Coghill, the embryologist, considers man as "a mechanism which within the limitations of life, sensitivity and growth is creating and operating himself." Moreover, as Bruch points out, obese children, whose problem also is largely a food problem, derive security satisfaction from the static fact of size alone. Our observations would seem to indicate that the peptic ulcer patient in his form and conduct is the very antithesis to this. His best hope for security seems to lie in eager effort, however futile or poorly directed, to recapture the conditions earlier provided by the maternal protectorate. And so his linear, streamlined body forms the most appropriate symbolization of the striving for complete virility.

CONCLUSIONS

From the correlated experience of experimental alimentary physiology, human psychology and the clinic, one may reasonably assert that the symptoms and perhaps also the lesions of peptic ulcer are associated with psychic traumata as definitely as with inappropriate food. Indeed it looks almost as though the food factor were secondary. From the patient's point of view, however, the obviousness of the relationship between what he eats and what he feels forces his own and his physician's chief attention upon food. As a result, it is exceedingly difficult to interest or persuade the patient, and occasionally also the doctor, that his malady may be other than a feeding one. The best proof of this is that even today the routine treatment of peptic ulcer in good hospitals and private offices revolves almost exclusively about the stomach itself. There are, of course, admonitions "not to worry" and to "take it easy." But these are not often specific nor persistently followed.

The latter point clearly leads to the difficult question of psychotherapy in peptic ulcer. Full discussion of this still controversial matter cannot be undertaken here. It may be said, however, that by and large neither deep nor simpler forms of psychotherapy have as yet produced striking results. Some individual cases have been helped, others have failed to respond at all. In this respect, the problem may not be unlike that recently discussed by J. D. Southerland¹² in his report of 100 cases of war neuroses. He develops the notion that certain personality weaknesses may be analogous to many organic ones which cannot be radically altered. If one accepts the notion that an ulcer-bearer's emotional pattern is a correlate of his other constitutional components one cannot expect to achieve much alteration of it. Careful study of the person, however, at least offers the possibility of discovering his reaction type and capacity and so assist in evaluating the degree and nature of environmental stress to which he can adjust.

In the treatment of the ulcer itself measures must be established to combat hyperacidity either by chemical means or by the selection of bland protein foods or milk. The psychological import of the latter is obviously to reestablish the expectations of the infant digestive organ. The basic view of ulcer here presented, however, assumes the organism's effort not to depart from and if possible even in adulthood, to regress to the protectorate of the mother principle. Indeed it appears as though the psychological panel of the ulcer patient had failed to mature. It is for this reason that because of the symbolic effects bed rest and frequent small feedings of milk, tended by a nurse, come into question. While such a plan may ease local distress, it can also, by virtue of its symbolic content, obstruct reestablishment of self-confidence and self-respect. Meulengracht's¹³ remarkably successful ulcer program, with meat in severe cases, even bleeding ones, would

¹² J. D. Southerland, *ibid.*

¹³ The ulcer program of this paper has frequently led to the following results: (1) a marked reduction of the physical reaction to the

peptic ulcer problem They are based on the belief that "'tis not the stomach but the man who's ill"

1 Only cases of severe hemorrhage and perforation to be admitted as ward patients At that stage such cases are emergency medical or surgical problems, like any other digestive tract accident of the sort

2 All other cases of peptic ulcer to be handled in the outpatient department

3 At the first interview an effort should be made to discover specific emotional traumata and the nature of the patient's individual reaction to them rather than maximum recording of dietetic indiscretions In regard to the former, the object is not to record a hard luck story and the adverse environment The nature of the patient's emotional response is the issue

4 Return appointments at short intervals for three or four interviews During these the patient may be helped to the realization of how much he himself has to do with his own malady Every effort to encourage self-respect and self-reliance is desirable, but it is usually difficult to alter the actual outside situation of a patient's life Moreover, it is always a question how much a patient should be helped directly by the physician and how much he should be required to do for himself Too much help tends to encourage the patient's unconscious effort to regress toward infancy

5 Antacid drugs may be used, but minimal emphasis on infant feeding and maximal on the establishment of adult fare is called for, even at the cost of slight discomfort

6 Before discharge following gastrectomy or operation for perforation, the patient should be turned over to the medical psychiatrist for reeducation planned to wean him from the mother principle and to reestablish his self-respect

7 The cure of peptic ulcer probably must be looked for through the inversion of those regressive psychobiological forces which engender it rather than by local treatment of the lesion itself

8 Peptic ulcer may turn out to be one of those widespread human afflictions which, like tuberculosis and cancer, can be controlled to a considerable extent by popular education directed at prevention through understanding

BIBLIOGRAPHY

- 1 DRAPER, G, and TOURAINE, G A The man-environment unit and peptic ulcer, Arch Int Med, 1932, xlix, 616
- 2 DRAPER, G, BRUENN, H G, and DUPERTUIS, C W Changes in the electrocardiogram as criteria of individual constitution derived from its physiological panel, Am Jr Med Sci, 1937, cxciv, 514-523
- 3 DRAPER, G The mosaic of androgyny, New England Jr Med, 1941, ccxxv, 393
- 4 CANNON, W B The influence of emotional states on the function of the alimentary canal, Am Jr Med. Sci, 1909, cxxvii, 480
- 5 PAYNE, R T, and NEWMAN, C Interim report on dyspepsia in the Army, Brit Med Jr, 1940, ii, 819

- 6 HUTCHINSON, J H Incidence of dyspepsia in a military hospital, Brit Med Jr, 1941, ii, 78
7. SPILLANE, J D Dyspepsia in the Army (Letter to the Editor), Brit Med Jr, 1941, i, 1933
- 8 HARTFALL, S J Dyspepsia in the Army (Letter to the Editor), Lancet, 1941, i, 124
- 9 SCHIFFER, P · The image and appearance of the human body, 1935, Kegan Paul, London
- 10 COGHILL, G E Anatomy and the problem of behavior, 1929, Cambridge University Press
- 11 BRUCH, HINDF Obesity in childhood and personality development, Am Jr Orthopsychiatry, 1941, xi, 467
- 12 SOUTHERLAND, D D Survey of 100 cases of war neuroses, Brit Med Jr, 1941, ii, 365
- 13 MEUFENGRACHT, E · Behandlung von Hematemesis und Melena mit uneingeschränkter Kot, Wein klin Wchnschr, 1936, xlix, 1481

SULFADIAZINE; A STUDY OF ITS EFFECT ON HEMOLYTIC STREPTOCOCCI *

By CHARLES H RAMMELKAMP, M D , and CHESTER S KEEFER, M D ,
F A C P , *Boston, Massachusetts*

IN view of the fact that patients with hemolytic streptococcal infections who are treated with sulfanilamide often continue to have a prolonged and protracted illness, it is desirable to search for more effective chemotherapeutic agents. Recently, another sulfonamide derivative, sulfadiazine, has been described by Roblin, Williams, Winnek, and English.¹ In preliminary studies it was found to protect mice against hemolytic streptococcal and pneumococcal infections.² Later,³ it was reported that it was superior to either sulfanilamide or sulfapyridine in the treatment of experimental infections of mice due to the hemolytic streptococcus. It was pointed out that the animals receiving sulfadiazine had a higher and more prolonged concentration of the drug in the blood and, therefore, the increased number of survivals in the infected mice might have been due to these factors.³

In man, the administration of sulfadiazine is followed by very few toxic effects. A recent report by Peterson, Strauss, Taylor, and Finland⁴ on the absorption, excretion, and distribution of sulfadiazine in tissues shows that it is absorbed readily from the gastrointestinal tract, and higher concentrations in the blood are reached and sustained longer than with sulfanilamide, sulfapyridine, or sulfathiazole. The conjugation of the drug is usually slight and there is no tendency for the drug to be retained in the body. Neither sodium sulfadiazine nor sulfadiazine was absorbed to any appreciable extent from the rectum. It will diffuse from the blood to the pleural or ascitic fluid and into the subarachnoid space in amounts varying from 50 to 94 per cent of the level in the blood. It was also noted by them that there was less nausea, vomiting, and mental depression following the use of this drug than exists following the other sulfonamides. These results are in agreement with those obtained by Sadusk and Tredway⁵ and Reinhold, Flippin, Schwartz, and Domm.⁶

The present study was undertaken to assess the relative activity of sulfadiazine and sulfanilamide against hemolytic streptococci in whole blood of normal individuals. We were also interested to obtain information concerning the concentration of sulfadiazine which produces a maximal effect.

METHODS

The methods of investigation were the same as we have described previously.⁷ Defibrinated whole blood from normal individuals was used.

* Received for publication June 9, 1941.

(Read before the Association of American Physicians, Atlantic City, N J, May 6, 1941.)

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

for media. The various drugs were added *in vitro* and the concentration determined by chemical analysis.⁵ In some of the experiments the drug was given by mouth, and samples of blood were withdrawn one, three, and four hours later. Determination of the concentration of the drug was then made on these samples.

In all, five different strains of hemolytic streptococci were used; three strains were isolated from the blood of patients with bacteremia, and two were isolated from the nasopharynx. They all showed beta hemolysis on blood agar plates and belonged to Lancefield's Group A. The organisms were stored on blood agar slants and a 12-hour peptone broth culture was used for the inoculations.

One-tenth c.c. of various saline dilutions of the test organism was added to 0.5 c.c. of the defibrinated blood containing varying concentrations of drug. Eight different dilutions of organisms were added to each sample of blood. The tubes were then sealed and rotated in the incubator for 24 hours. The contents of the tubes showing no hemolysis were plated out and the colonies counted. In those tubes showing hemolysis the number of organisms present varied between 10^{-7} and 10^{-8} per c.c.

EFFECT ON THE KILLING POWER OF WHOLE BLOOD FOLLOWING ADMINISTRATION OF SULFADIAZINE BY MOUTH

In these experiments samples of blood were withdrawn before and three hours after the administration of 4 gm. of sulfadiazine by mouth. These two samples of blood were then used as culture media as described above.

Thirty experiments were performed, table 1 shows the results of five

TABLE I
Effect of Sulfadiazine on Whole Blood after Its Administration by Mouth to Normal Individuals

Experiment	Culture Media	Dilution of Culture						
		10^1	10^2	10^3	10^4	10^5	10^6	10^7
1	Whole blood	4	+	+	+	+	0	2
	Whole blood plus S.D.	2	0	0	0	0	0	
	Whole blood plus 100 cc.	4	—	+	+	+	0	2
	Whole blood plus S.D.	13	0	0	0	0	0	
	Whole blood plus 100 cc.	4	+	+	+	+	0	
	Whole blood plus S.D.	0	1	0	0	0	0	
	Whole blood plus 100 cc.	4	+	+	+	+	+	
	Whole blood plus S.D.	16	0	0	0	0	0	
	Whole blood plus 100 cc.	—	+	+	+	+	10	1
	Whole blood plus S.D.	0	0	0	0	0	0	

* 4 = 4 colonies per 0.1 c.c. of culture; + = 10 to 100 colonies per 0.1 c.c. of culture; — = no colonies per 0.1 c.c. of culture; 0 = no colonies per 0.1 c.c. of culture.

such experiments which are typical examples of the group as a whole. The concentration of free sulfadiazine in the blood varied from 2.6 to 10 mg per 100 c.c. In every instance a bactericidal effect was observed. From these results it was clear that administration of sulfadiazine by mouth to normal individuals increased the bactericidal action of normal blood against hemolytic streptococci. This is in striking contrast to our previous studies with sulfanilamide,⁸ in which a bactericidal effect was observed only when natural antibodies were present, or when a very small number of organisms was used in the inoculum.

In figure 1, the results of giving a single dose of 5 grams of sulfadiazine by mouth to three normal individuals are shown. The bactericidal power

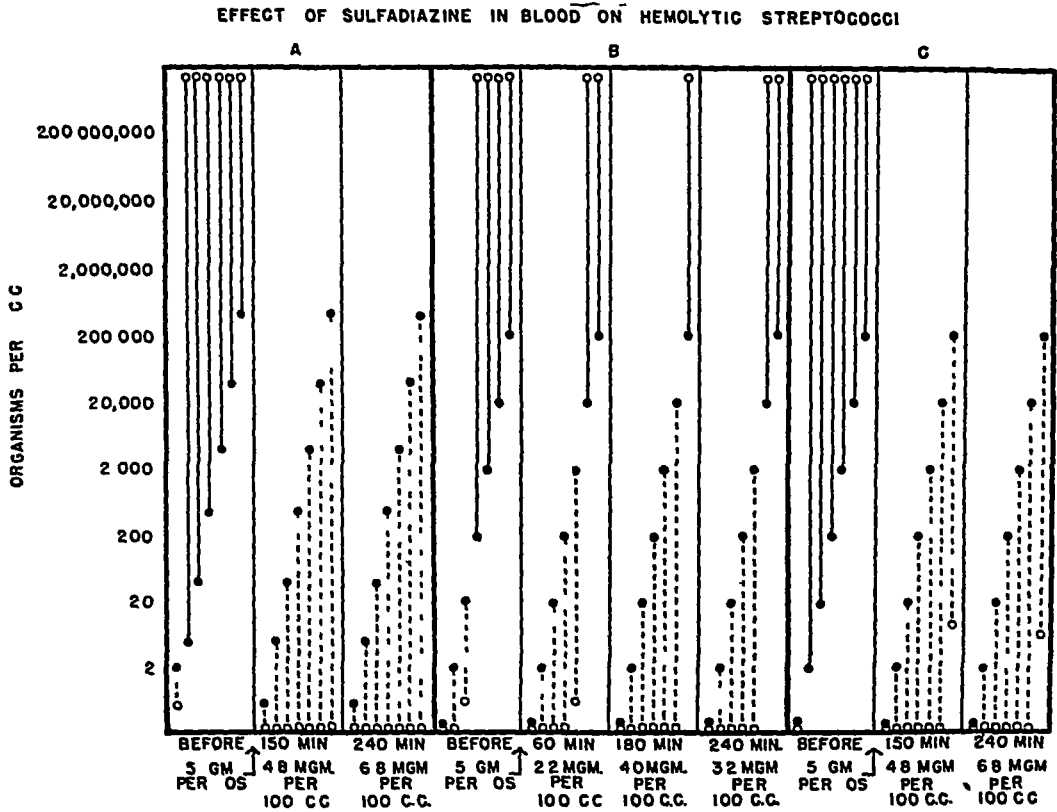


FIG 1 The solid dots indicate the number of organisms in the inoculum, the circles, the number of organisms after 24 hours' incubation

of the blood was tested before the exhibition of the drug, and then at varying periods of time blood was obtained for chemical and bactericidal tests. In all three individuals a bactericidal effect was observed when sulfadiazine was present in concentrations varying from 2.2 to 6.8 mg per 100 c.c. These experiments show that sulfadiazine increases the bactericidal power of the blood against the hemolytic streptococcus when it is given by mouth.

EFFECT OF VARYING CONCENTRATIONS OF SULFADIAZINE IN BLOOD FOLLOWING ORAL ADMINISTRATION

We then determined the concentration of drug which would produce the maximal effect. Figure 2 shows the results obtained in 10 normal individuals. In these experiments blood was withdrawn before sulfadiazine was administered and at varying intervals thereafter. All samples of blood were stored in the icebox until the last specimen was taken.

The concentration of free sulfadiazine in the blood varied from 0.8 mg. per 100 cc. to 10 mg. per 100 cc. In the blood sample containing 0.8 mg. per 100 cc. there was a definite increase in the killing power. When

BACTERICIDAL EFFECT OF VARIOUS CONCENTRATIONS OF SULFADIAZINE
FOLLOWING ORAL ADMINISTRATION

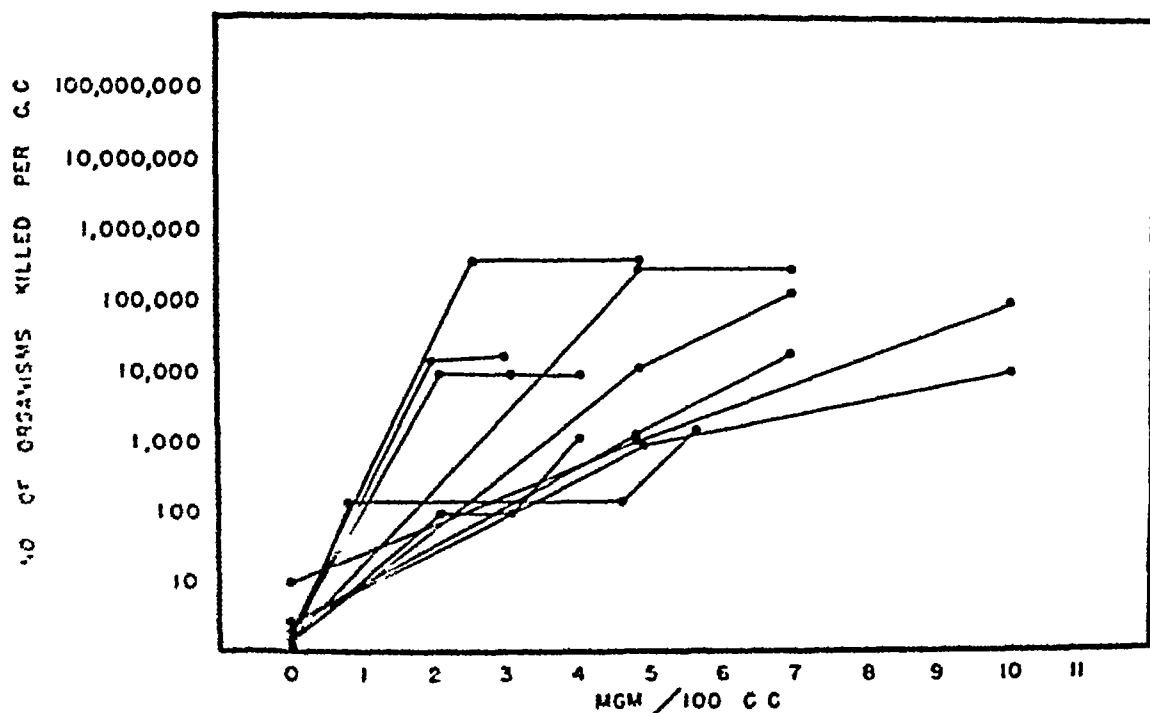


FIG. 2. Solid dots represent number of organisms present after 24 hours' incubation.

the concentration was raised to 5.6 mg. per 100 cc., a greater increase in the killing power was observed. These experiments demonstrate, then, that as the concentration of sulfadiazine in the blood is increased there is an associated increase in the bactericidal power of the blood against the hemolytic streptococcus. Maximal effects were observed when a concentration of 4 to 5.6 mg. per 100 cc. or higher was obtained.

A comparison of the bactericidal power of a sample of whole blood containing 10% antihemolytic and one without any antihemolytic following the addition of 10% sulfadiazine is shown in figure 3. It is plain that sample A (control) is much more bactericidal than sample B.

When the concentration of sulfadiazine was 3.0 mg. per 100 cc., 1.2 x 10⁶

hemolytic streptococci per cubic centimeter of blood were killed. In sample B, which contained no antibody, only 1,000 organisms were killed when the concentration was 4 mg per 100 c c. This striking difference was due to the presence of antibody in one specimen of blood and its absence in the other. It is seen, then, that sulfadiazine greatly enhances the bactericidal effect of whole blood containing antibody and that this is evident even when low concentrations of the drug are used.

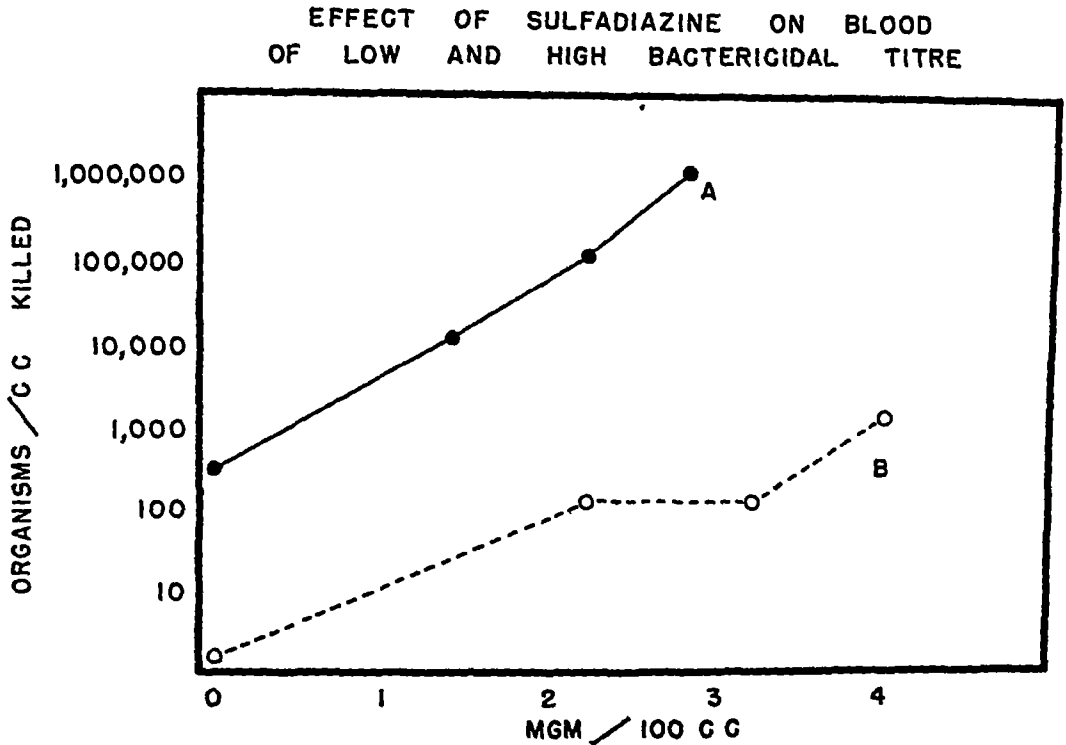


FIG 3 Blood A is the sample in which 600 organisms were killed without sulfadiazine

COMPARATIVE EFFECT OF SULFANILAMIDE AND SULFADIAZINE WHEN ADDED TO WHOLE BLOOD IN VITRO

Inasmuch as it was demonstrated that sulfadiazine was bactericidal for the hemolytic streptococcus, we then turned our attention to the study of the relative merits of sulfanilamide and sulfadiazine in whole blood. The following procedures were carried out:

Blood was obtained in 150 c c amounts from normal individuals and defibrinated. To two 24 c c samples of this blood 5 mg of powdered sulfadiazine and sulfanilamide respectively were added and thoroughly mixed for one hour. These two samples were then diluted with the blood so that varying concentrations of drug were obtained. These concentrations were then checked by chemical analysis. Eight dilutions of the test organism were added to each concentration of blood containing the two drugs. After

24 hours' incubation the number of organisms was determined as outlined above.

Figure 4 shows the results obtained in one of these experiments. When the original inoculum was 240,000 organisms per cubic centimeter of blood, the growth of organisms was not affected by either sulfanilamide or sulfadiazine until the concentration of the drug was above 10 mg per 100 cc. At the higher concentrations there was definite killing in the blood con-

COMPARATIVE BACTERICIDAL ACTION OF SULFANILAMIDE AND SULFADIAZINE
ADDED IN VITRO TO BLOOD

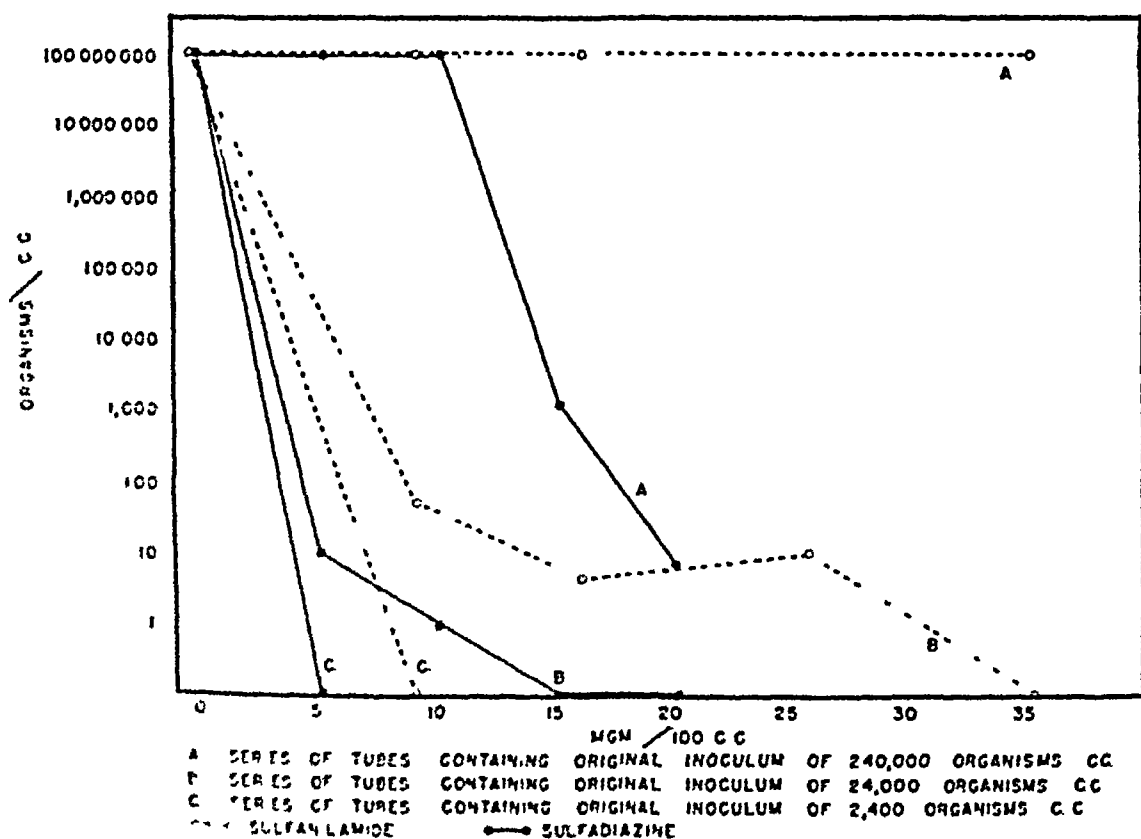


FIG. 4. Plot represents the number of organisms per cubic centimeter present after 24 hours' incubation.

tain, sulfadiazine (Experiment A). When small inocula were used, both the sulfanilamide and sulfadiazine-containing cultures exhibited a definite bactericidal action, although there was a tendency for the blood containing sulfadiazine to exhibit killing at lower concentrations (Experiments B and C).

DISCUSSION

In the above experiments it is shown that sulfadiazine is a powerful bactericidal agent when it is tested against hemolytic streptococci. This bactericidal effect is obtained when the drug was added directly to whole defibrinated blood. It is not clear whether it acts directly or indirectly on the bacterial

effect was present in dilutions as low as 2 to 5 milligrams per 100 c c, and it was enhanced by the presence of natural or acquired antibodies. When the relative merits of sulfanilamide and sulfadiazine were compared in vitro, it was clear that sulfadiazine was always more effective in killing hemolytic streptococci.

The evidence at present is suggestive that sulfadiazine will be superior to sulfanilamide in the treatment of hemolytic streptococcal infections in man. Since it is relatively non-toxic and is readily absorbed from the gastrointestinal tract and diffuses into the serous sacs and meninges in high concentration, it would seem to be preferable to sulfanilamide in the treatment of hemolytic streptococcal infections.

SUMMARY AND CONCLUSIONS

1 Sulfadiazine is bactericidal for the hemolytic streptococcus when the inoculum is small and the concentration is between 2 and 5 mg per 100 c c.

2 Its action is enhanced by the presence of antibactericidal antibody, either natural or acquired.

3 When sulfadiazine is compared with sulfanilamide, it is found to be superior insofar as its bactericidal effect is concerned, and it is more effective as a bacteriostatic agent in lower dilutions.

REFERENCES

- 1 ROBLIN, R. O., JR., WILLIAMS, J. H., WINNEK, P. S., and ENGLISH, J. P. Chemotherapy II. Some sulfanilamido heterocycles, *Jr. Am. Chem. Soc.*, 1940, **lxii**, 2002.
- 2 ROBLIN, R. O., JR., and WINNEK, P. S. Chemotherapy I. Substituted sulfanilamidopyridines, *Jr. Am. Chem. Soc.*, 1940, **lxii**, 1999.
- 3 FEINSTONE, W. H., WILLIAMS, R. D., WOLF, R. T., HUNTINGTON, E., and CROSSLEY, M. L. The toxicity, absorption and chemotherapeutic activity of 2-sulfanilamidopyrimidine (sulfadiazine), *Bull. Johns Hopkins Hosp.*, 1940, **lxvii**, 427.
- 4 PETERSON, O. L., STRAUSS, E., TAYLOR, F. H. L., and FINLAND, M. Absorption, excretion and distribution of sulfadiazine (2-sulfanilamidopyrimidine), *Am. Jr. Med. Sci.*, 1941, **cci**, 357.
- 5 SADUSK, J. F., JR., and TREDWAY, J. B. Observations on the absorption, excretion, diffusion, and acetylation of sulfadiazine in man, *Yale Jr. Biol. and Med.*, 1941, **xiii**, 539.
- 6 REINHOLD, J. G., FLIPPIN, H. F., SCHWARTZ, L., and DOMM, A. H. The absorption, distribution, and excretion of 2-sulfanilamido pyrimidine (sulfapyrimidine, sulfadiazine) in man, *Am. Jr. Med. Sci.*, 1941, **cci**, 106.
- 7 RAMMELKAMP, C. H., and KEEFER, C. S. Sulfathiazole effect on *Staphylococcus aureus* in vitro, *Proc. Soc. Exper. Biol. and Med.*, 1940, **xliii**, 664.
- 8 KEEFER, C. S., and RANTZ, L. A. Sulfanilamide: a study of its mode of action on hemolytic streptococci, *Arch. Int. Med.*, 1939, **lxiii**, 957.

RESPONSE TO SULFAPYRIDINE IN 241 CASES OF PNEUMONIA, WITH ESPECIAL REFERENCE TO LACK OF PROMPT RESPONSE IN SOME CASES

By SIDNEY SCHERLIS, M D , *Baltimore, Maryland*

THIS paper deals with a series of 241 unselected cases of pneumonia treated with sulfapyridine in 1938-1939 and 1939-1940. This group, although not numerically impressive, is reported because the patients were followed closely and studied carefully, and because an analysis of those cases in which sulfapyridine was not promptly effective yields hitherto unemphasized information of value.

DISTRIBUTION OF CASES

The cases reviewed total 241, and are consecutive and unselected save for the omission of a few that were admitted moribund and died within less than 24 hours after admission. Of the series, 73 were seen in the winter of 1938-1939, and 168 in the winter of 1939-1940. There were 129 males and 112 females. The age distribution of the group is shown in table 1. There were 21 deaths and 13 autopsies in the group, with a mortality rate of 8.7 per cent for the series.

METHOD OF TREATMENT

In most of these cases treatment with sulfapyridine was started within four days of the onset of the pneumonia. All of the patients except a few very young infants had an initial blood culture before chemotherapy was started, and in the initial blood culture was positive, blood cultures were repeated daily until they were repeatedly negative. Sputum was studied by the Neufeld technique and culturally, by the injection of mice and the subsequent Neufeld examination of the peritoneal exudate if the pneumococci originally found were not typable with the Neufeld quellung reaction.

The usual oral dosage of sulfapyridine for adults was an initial dose of 2 gm., then 1 gm. every four hours for two days, and then 1 gm. every six hours, with gradual reduction of the dose, until it was discontinued after the temperature had remained normal for five days. In children the dose was correspondingly smaller, averaging 1½ grains per pound of body weight in 24 hours. The initial dose of about one-half the calculated daily total. In children the dose was stopped after the temperature had remained normal for five days. Blood counts were even in patients cured by the sulfapyridine treatment, and in the majority of the cases in the first few days of treatment.

for the first few days and then less frequently in most cases, with adjustment of the dosage if it was felt that the blood level was not high enough. In most cases the average concentration of total sulfapyridine (Marshall's method) in the blood was between 4 and 7 mg per cent. All patients had daily urinalysis, daily estimation of hemoglobin and leukocyte and differential blood counts.

No effort was made to restrict the total fluid intake, fluids being forced to a high total daily intake in most cases.

TABLE I
Age Distribution of Cases and Deaths

Age (Years)	No. Cases	Deaths (Age)
Less than 1	22	7, 8, 8 (mos)
1	16	12, 13, 13, 18, 18 (mos)
2	7	
3	9	
4	4	
5	8	
6	9	
7	8	7 (yrs)
8	4	
9	0	
10	2	
11	3	
12	1	
13	4	
14	4	14 (yrs)
15	4	
16-20	11	
21-25	12	
26-30	10	
31-35	11	
36-40	13	
41-45	6	
46-50	8	
51-55	12	55 (yrs)
56-60	14	59, 60 (yrs)
61-65	11	62 (yrs)
66-70	18	67, 67, 69 (yrs)
71-75	5	71 (yrs)
76-80	5	77, 78, 79 (yrs)
Totals	241 Cases	21 Deaths

RESPONSE TO SULFAPYRIDINE

Of the 241 cases treated, 21 died and 220 recovered. Most of the patients who recovered responded with a drop of temperature to a normal level, subsequently maintained, within 48 hours after administration of sulfapyridine was started. We shall refer to this group as those responding by "crisis." There were 173 in this "crisis" group. The remaining 47 cases showed no such dramatic drop of temperature, and seemed not to respond to the chemotherapy. This latter group will be referred to as the "lysis" group. In this paper we are interested chiefly in an analysis of the "lysis" group, in order to discover why these 47 cases did not respond to treatment promptly or at all.

1 Distribution of the Pneumonia The cases were classified as either lobar pneumonia or bronchopneumonia, depending upon whether the physical signs were those of massive or of patchy consolidation and upon the roentgen-rays which were taken in many cases. According to this classification, which is admittedly arbitrary, the cases were distributed as follows:

Response	Distribution of Pneumonia		Total
	Lobar	Broncho	
Crisis	94	79	173
Lysis	12	35	47
Total	106	114	220

It is seen that failure to respond promptly was much more frequent among the cases with patchy involvement than in those with true lobar consolidation. And again, of those failing to respond promptly only one-fourth had true lobar involvement, other factors being equal. In most cases the number of lobes involved was apparently not directly related to response to sulfapyridine.

2 Etiology of the Pneumonia It was thought that the failure to respond to treatment might be due not so much to the type of anatomical distribution as to the different bacteria responsible for the lobar or the bronchopneumonia. The cases were, therefore, classified according to etiology and response to treatment as follows:

Sputum	Termination by		
	Crisis	Lysis	Death
Typable pneumococci	68	15	11
Pneumococci of no known type	30	5	—
Proteus (Serratia) - Strep.	1	—	—
Pneum. - Staph. - Strep.	17	3	2
Pneum. - Staph.	22	6	2
Staph. pneumoniae - flex. Pneumo.	2	7	—
Staph. pneumoniae	10	7	2
Proteus - Staph.	2	2	—
Staph. - Staph.	13	1	3
Staph. pneumoniae - flex.	1	—	1
Total	175	47	21

A review of this chart shows that in the predominating organism in the pneumoniae—the pneumococci (168 cases), most of the patients responded promptly to treatment (crisis, 141; lysis, 27), but if staphylococci or streptococci were present (52 cases), a greater proportion did not respond promptly to sulfapyridine (crisis, 32; lysis, 2).

Since the organisms which did not respond promptly to treatment were more numerous in the patchy type of pneumonia, the effect of the type of anatomical distribution on the response to treatment, with the full dose of

Complication	Lobar	Lysis	Broncho-
Spread	1		1
Bacteremia	2		1
Marked pleurisy	1		—
Pleural effusion	2		2
Empyema	2		—
Unresolved pneumonia	—		1
Otitis media	—		3
Mastoiditis	—		2
Severe nausea and vomiting	—		3
Drug rash	1		1
Hematuria	1		2
Toxic neuritis	—		1
Totals	10		17

Thus, of 12 cases of lobar pneumonia which did not respond promptly, 10 had complications as listed, of 35 cases of bronchopneumonia which did not respond promptly, 17 had complications. In this series complications were more frequent among the cases of lobar pneumonia which did not respond than among the cases of bronchopneumonia which did not respond.

COMPLICATIONS OF SULFAPYRIDINE THERAPY

Nausea and vomiting occurred frequently after the administration of sulfapyridine, but in only a small number of cases were they severe enough to necessitate discontinuing the use of the drug. Other complications met with in this series were

Complications	No. Cases
Drug rash	4
Microscopic hematuria	8
Gross hematuria	6
Gross hematuria, with abdominal pains	1
Moderate hemolytic anemia	2
Marked drop in total WBC	
To 5000 cells	1
To 4000 cells	1
To 1600 cells	1
Toxic neuritis	1
Total	25

None of the complications listed deserves particular consideration except perhaps a toxic neuritis that developed. This occurred in a 29 year old white male with Type III bronchopneumonia. His temperature fell gradually after the administration of sulfapyridine was started, reaching a normal level six days later. During convalescence he showed signs of a neuritis of the terminal filaments of the right ulnar and musculocutaneous nerves. This improved gradually but was still present at the time of his discharge.

COMPLICATIONS OF PNLUMONIA

The complications met with in this series total 30, consisting of 16 cases of otitis media, three cases of mastoiditis, nine cases of pleural effusion and two cases of empyema

1 *Otitis Media* Of the 16 cases of otitis media, nine were present on admission and seven were noted later Most of these required myringotomy Response to sulfapyridine was prompt in 12 cases The presence of otitis was apparently not related to the duration of the disease on admission, nor to the blood sulfapyridine level Practically all of the cases occurred in children, and in only one case was there a typable pneumococcus in the sputum—Type XXII The aural discharge contained hemolytic *Staphylococcus albus* or *aureus* in most cases, except for one case in which a few streptococci were also present

2 *Mastoiditis* Mastoiditis occurred in three infants, aged 8 months, 9½ months, and 18 months, respectively In only one case was response to sulfapyridine prompt There was no apparent relation to the duration of the disease on admission, nor to the blood sulfapyridine level Mastoidec-tomy was performed in all three cases, with recovery in all The cultures from the mastoids at operation yielded hemolytic *Staphylococcus aureus* in two cases, and pneumococcus in one case

3 *Pleural Effusion* Of the nine cases of pleural effusion, four were noted on admission and five were discovered later Thoracentesis was per-formed in six cases, and cultures of all of the fluids were sterile There was prompt response to sulfapyridine in five of the nine cases The sputum showed typable pneumococci in five cases Types I, III, VII, VIII, XII The ages of the patients were 6, 7, 16, 18, 29, 29, 33, 45, and 59 years, respectively The presence of the pleural effusion was apparently not related to the duration of the disease on admission, nor to the blood sulfapyridine level

4 *Empyema* There were two cases of empyema among the 220 cases which recovered One of these was in a 42 year old white female with Type II pneumonia involving the left lower lobe and right middle and lower lobes Her temperature at the time of admission showed one to three colonies Type III pneumococcus per c.c This patient had a poor response to specific serum therapy (260,000 units on third and fourth days of disease) and the sulfapyridine concentration reached 40 mg per cent Temperature fell to 99° F and then rose again and remained elevated Thoracentesis on the 15th day yielded 10 c.c of cloudy fluid which was sterile on culture and the sulfapyridine was discontinued, and the blood sulfapyridine concentration rose to 10 mg per cent Thoracentesis on the twentieth day yielded 10 c.c of turbid fluid, containing Type II pneumococci The patient recovered without surgery for empyema which subsided in 10 days and the patient was discharged on the 25th day

The second patient with empyema did not require operation. He was a 32 year old white man admitted on the fifth day of his disease with pneumonia of the left lower and right lower lobes. Sputum showed Type XXII pneumococcus. Repeated blood cultures were negative. Sulfapyridine treatment was started on admission, the blood level reaching 10 mg per cent. Temperature gradually fell during the first five days of treatment, then rose on the eighth day, and sulfapyridine was discontinued. Temperature was normal by the thirteenth day after admission and remained so. On the fourth day after admission thoracentesis yielded 40 c c of cloudy fluid which contained Type XXII pneumococcus. This fluid became sterile later, as shown in the following table.

Day of Treatment	c c.	Cells per cu mm	Culture	Sulfapyridine Conc Mg %	
				Blood	Pleural Fluid
4	40	1800 (L-24, P-76)	Type XXII		
6	15	1950 (L-19, P-81)	Sterile	8.3	6.2
7	200	1050 (L-36, P-64)	Sterile	10.0	7.1
9	20	2050 (L-22, P-78)	Sterile		
11	—	— (—)	Sterile		

BACTEREMIA

In the entire series of 241 cases, there were 13 cases with bacteremia. Of these, three died, one developed empyema requiring thoracotomy, two had sterile pleural effusions, and one had delayed resolution. Three had a prompt response to sulfapyridine, nine showed a delayed response if any, and three died. The types of pneumococci found in the blood were Type I in four cases, Types II, III, XIV and XVIII in one case each, and Type VII in two cases.

DEATHS

There were 21 deaths in the series of 241 patients treated with sulfapyridine, a mortality of 8.7 per cent for the group. The age distribution of these cases is shown in table 1. There were eight deaths in children under 18 months of age, and 11 deaths in adults 55 years of age or older, with only two deaths in the group between three and 55 years of age, i.e., mortality rates of 21.0 per cent, 16.9 per cent, and 1.4 per cent, respectively. The important findings in each of the fatal cases are summarized in table 2. Only two of the fatal cases occurred in patients who were not very young or very old. One of these was a seven year old child admitted late in the course of the disease, with Type XVIII pneumococcus in his sputum, pneumonia of the entire right lung on admission, and empyema on the right due to Beta hemolytic streptococci. The other was a 14 year old child with

TABLE II
Summary of Findings in Fatal Cases

No	Age	Sputum	Remarks—Autopsy
1	7 Mos	Type XIV Pneumo	224 Colonies per c c on admission blood culture Bilateral otitis media on admission, yielding Beta hemolytic streptococcus Given 2 c c Type XIV rabbit serum two hours before death on second hospital day Autopsy Lobar pneumonia, right lower lobe Acute fibrino-purulent pleurisy, right, yielding Type XIV pneumococci on culture Pleural effusion, right, small
2	8 Mos	Type XXIX Pneumo	Negative blood culture Died on fifth day in hospital after initial crisis and afebrile period of two days Received very small sulfapyridine dosage after first day of treatment Autopsy Pneumonia of all five lobes Small amount fibrinopurulent pleurisy
3	8 Mos	Type XXIII Pneumo	No blood culture obtained Admitted on third day of disease and died on following day Cyanotic on admission Autopsy Heart blood sterile Bilateral bronchopneumonia Pleural effusion on right, 300 c c sero-sanguinous fluid Pleura of both lungs normal Culture of pleural fluid and of secretion in right bronchus yielded pure Alpha hemolytic streptococci
4	12 Mos	Hem strep Non-hem staph	Blood culture sterile Admitted with otitis media and malnutrition Signs of pneumonia appeared on sixth day in hospital Received 0.4 gm sodium sulfapyridine intravenously, blood level reaching 10.1 mg per cent. Died on seventh day in hospital Autopsy Lobar pneumonia, right and left lower lobes Pleural effusion, bilateral Acute serous mastoiditis, bilateral (streptococci cultured on right side)
5	13 Mos	Pneumo Staph	Blood culture sterile Admitted on second day of disease, received sulfapyridine immediately, concentration reaching 7.7 mg per cent next day Temperature dropped to normal within 24 hours after treatment was started On second hospital day child died suddenly while being fed. Autopsy Bronchopneumonia of entire right lung Atelectasis of left lower lobe Widespread congenital deformities of genitourinary system
6	13 Mos	Pneumo Staph Strep	Blood culture sterile Admitted on first day of disease, treatment with sulfapyridine started immediately Blood level not obtained Initial drop in temperature, rising again irregularly to 107° and 108° F at death on third hospital day Had recovered from mumps two weeks before Autopsy Acute bilateral lobular pneumonia involving all lobes, especially right upper lobe Pleura normal Postmortem pleural and lung culture yielded <i>Staphylococcus albus</i> and <i>B. pyocyaneus</i>
7	18 Mos	Not obtained	Blood culture and sputum not obtained Admitted and treatment started on fourth day of disease, blood level of 6.5 mg per cent sulfapyridine reached Bronchopneumonia of left upper and left lower lobes No response to sulfapyridine, with gradual downward course Thoracentesis (left) on second hospital day yielded small amount of fluid which yielded hemolytic <i>Staphylococcus aureus</i> in culture Child died on fourth day in hospital No autopsy.

TABLE II—Continued

No	Age	Sputum	Remarks—Autopsy
8	18 Mos	Pneumo Few staph	Admitted with influenzal meningitis of 2 to 3 days' duration Small areas of bronchopneumonia noted Received 20 c c of anti-influenzal serum Also received sulfapyridine orally and sodium sulfapyridine intravenously, the latter being followed by convulsions for 8 hours, yielding only to ether No response to treatment Autopsy Acute purulent meningitis, yielding <i>Hemophilus influenzae</i> in culture Bilateral bronchopneumonia
9	7 Yrs	Type XVIII Pneumo	Admitted moribund after illness of 2 weeks at home, treated inadequately at home with sulfapyridine (blood level too low to read on admission) Blood culture sterile, with pneumonia of entire right lung on admission Empyema, right, on admission, yielding Beta hemolytic streptococci in culture Received sulfapyridine and intravenous sulfanilamide Course steadily downward, patient dying 36 hours after admission
10	14 Yrs	Hem <i>Staph aureus</i>	Admitted on second day of disease with involvement of right lower lobe, very toxic Received sulfapyridine orally and intravenously, blood level reaching 14.3 mg per cent No response to treatment, dying day after admission Postmortem lung puncture fluid yielded no pneumococci on mouse injection, showed great numbers of staphylococci on smear
11	55 Yrs	Pneumo Non-hem staph	Bronchopneumonia left lower lobe on admission on fifth day of disease, received sulfapyridine immediately, level of 9.1 mg per cent reached Temperature became normal on fourth day for 24 hours, then rose coincident with signs of spread to more of left lung and to right base Died on sixth hospital day Diabetic hypertensive with cardiac enlargement, azotemia, anginal syndrome
12	59 Yrs	Strep Staph Few Pneumo	Blood culture sterile Admitted on second day of disease, received sulfapyridine immediately, blood level of 4.4 mg per cent reached No response to drug Hypertensive with cardiac enlargement Died on fifth hospital day Autopsy Pleural effusion, left, 1000 c c, watery, sanguinous Right effusion 100 c c
13	60 Yrs	Type III Pneumo	Blood culture sterile Admitted on second day, given sulfapyridine, blood level not obtained Bronchopneumonia both bases Initial fall in temperature, which promptly rose again, together with rise in blood sugar to 400 mg per cent despite increase in insulin Died after two days in hospital Diabetic Positive Wassermann Arteriosclerotic cardiovascular disease Several previous attacks Type III pneumonia
14	62 Yrs	Type I Pneumo	Admission blood culture 2000 colonies per c c Admitted on sixth day of disease, sulfapyridine started immediately, blood level of 5.3 mg per cent reached Died 36 hours after admission Autopsy Pneumonia of all five lobes
15	67 Yrs	Type I Pneumo	Blood culture sterile Admitted on seventh day of disease, treatment started, blood level of 3.2 mg per cent obtained Toxic, cyanotic on admission Given 120,000 units Type I horse serum day after admission No response Died day after admission Autopsy Lobar pneumonia, left upper lobe Acute fibrinous pleurisy, left Aortic stenosis and insufficiency due to arteriosclerosis Chronic miliary tuberculosis of both lungs, adrenals, mediastinal, hilar and tracheobronchial lymph glands

TABLE II—Continued

No	Age	Sputum	Remarks—Autopsy
16	67 Yrs	Type XIX Pneumo	Blood culture sterile Admitted on first day of disease with pneumonia and meningitis and otitis sulfapyridine, concentration in blood reaching 8.7 mg per cent, and 300,000 units Type XIX horse serum Course downward, dying three days after admission Type XIX pneumococcus cultured from ear, spinal fluid, and postmortem lung Autopsy Lobar pneumonia, left lower Acute fibrinous pleurisy, left Acute purulent meningitis Carcinoma left breast. Arteriosclerotic heart disease.
17	69 Yrs	Type III Pneumo	Blood culture in broth yielded Type III pneumococcus on admission Duration of disease unknown, with pneu- monia of left upper and lower lobes on admission Blood sulfapyridine level 7.6 mg per cent Initial response with later rise in temperature, and increasing cardiac embarrassment Died on fourth hospital day. Decom- pensated arteriosclerotic cardiovascular disease, with azotemia
18	71 Yrs	Type XI Pneumo	Blood culture sterile Pneumonia both lower lobes on admission on second day of disease Initial response to sulfapyridine with blood level of 5.7 mg per cent Pneumonia spread and temperature rose as sulfapyridine dose was reduced and concentration became too low to read on fifth hospital day Died on ninth day in hospital. Arteriosclerotic and hypertensive cardiovascular disease
19	77 Yrs	Hem <i>Staph.</i> <i>aureus</i> Few strep	Treatment started on admission on seventh day of disease, with prompt drop in temperature Temperature rose again after being normal 8 days, but this time there was no response to sulfapyridine, temperature gradually falling after 5 more days A third time the temperature rose, spiked, and did not respond at all to sulfapyridine Bronchoscopy during third febrile episode showed congested mucosa Autopsy Bronchopneumonia right lower lobe Bronchiectasis with many cavities, both lower lobes, right upper lobe Pulmonary tuberculosis, inactive Marked pleural and pericardial adhesions Arteriosclerotic kidney disease
20	78 Yrs	Type III Pneumo	Blood culture sterile Admitted on fourth day of disease, sulfapyridine started immediately, blood level of 10.2 mg per cent reached Initial drop of temperature to normal in 48 hours, then rose again, patient dying on twelfth day of disease Autopsy Pneumonia right upper and lower lobes, left lower lobe Alcoholic cirrhosis of liver, coronary sclerosis, myocardial scars, arteriosclerotic nephrosclerosis
21	79 Yrs	Staph Strep Pneumo	Blood culture sterile Admitted on fifth day, treatment started, and blood level of 5.2 mg per cent reached, with temperature dropping to normal within 36 hours Bronchopneumonia of both bases Temperature remained normal, and patient died suddenly in pulmonary edema on ninth day in hospital after being up one day Ar- teriosclerotic cardiovascular disease

probably staphylococcal pneumonia of the right lower lobe, admitted on the second day of the disease and dying the following day

SUMMARY

1 The results of the treatment of a series of 241 cases of pneumonia with sulfapyridine with 21 deaths have been recorded and analyzed

2 An attempt has been made to explain the failure of some cases to respond promptly to sulfapyridine

3 The data emphasize the value of the drug in the treatment of pneumococcal pneumonia and indicate some of the hazards incident to its administration

THE CARDIOVASCULAR ASPECTS OF CAROTID SINUS HYPERSENSITIVITY WITH SPECIAL REFERENCE TO SOME CARDIAC ARRHYTHMIAS¹

By ALLEN D TANNEY, M D, and ALFRED LILIENFELD, M D,
New York, N Y.

THE effects of carotid sinus hypersensitivity on the cardio-vascular system are well known^{1,2} Most of the case records are concerned with patients who had a basic normal sinus rhythm whereas only a limited number of reports could be found wherein carotid sinus hypersensitivity was associated with cardiac arrhythmia Weiss and Baker¹ reported one case with auricular fibrillation (in this patient carotid sinus stimulation produced only slight slowing of the ventricular rate) and Hiatt and Adams³ published the record of one patient with auricular flutter A survey of the literature failed to reveal the association of paroxysmal tachycardia and carotid sinus hypersensitivity

Recently the opportunity was presented to observe four instances of carotid sinus hypersensitivity, each occurring in a different cardiac rhythm, viz regular sinus rhythm, paroxysmal auricular tachycardia, auricular fibrillation and auricular flutter It is interesting to note that these four cases were first seen at the New York Post-Graduate Hospital within a period of two weeks

Case 1 A 58-year-old Jewish dressmaker was admitted to the New York Post-Graduate Hospital on April 1, 1940 on the service of Dr John D Currence Two weeks prior to admission the patient had what he described as an "upset stomach" At that time he had a large meal following which he felt bloated He took some salts and almost immediately felt dizzy and vomited This was followed by a feeling of generalized warmth and subsequent relief He felt well for a week when, after another heavy meal, he felt nauseated and dizzy with a desire to defecate While at stool, he became faint but did not lose consciousness The next day he consulted a local physician who told him he had a weak heart and prescribed one and one-half grains of digitalis daily, which the patient took up to the day of admission There was no history of dyspnea, orthopnea, cough, palpitation or peripheral edema Forty years before, a fistulo-in-ano had been excised and 26 years before, a plastic operation had been performed on his eyelids for bilateral ptosis Otherwise his past history and family history were irrelevant

The physical examination showed a well developed, well nourished male lying comfortably in bed, not evidently ill A lipoma the size of an egg was present on the posterior aspect of the scalp The pupils were equal, regular, and reacted to light and accommodation The throat and neck were negative The chest was emphysematous in type, the heart was not enlarged The heart sounds were of fairly good quality

* Received for publication March 3, 1941

From the Department of Medicine, Division of Cardiology, New York Post-Graduate Medical School and Hospital, Columbia University, New York

with regular sinus rhythm, rate 60 per minute. No murmurs were heard. Blood pressure was 126 mm Hg systolic and 90 mm diastolic. The lung fields were clear. No organs or masses were felt in the abdomen. The reflexes were physiological.

Laboratory Studies Examination of the urine was negative. The complete blood count was essentially normal. Wassermann and Kahn tests were negative. The blood chemistry was normal. An electrocardiogram showed slight left axis deviation. Roentgen-rays of the gastrointestinal tract revealed a rather marked antral spasm but no evidence of intrinsic gastric lesion.

Course On the second day of his hospital stay, while straining at stool, the patient suddenly felt nauseated and then vomited. He felt weak and dizzy and was aware of a sense of fullness in his head.

The electrocardiographic effects of carotid sinus pressure with the patient in the recumbent position are illustrated in the accompanying tracings, all of which were taken in Lead II. Within one half second after pressure was applied on the right carotid sinus, complete cardiac standstill was produced for a period of 5.2 seconds. The initial beat of recovery was nodal in origin, succeeded by normal sinus mechanism (figure 1b). Pressure on the left carotid sinus produced almost identical results with a complete standstill of 4.4 seconds (figure 1c).

During the procedure, the patient complained of nausea, with a sense of fullness in the head. His face blanched and beads of perspiration covered his brow. Loss of consciousness rapidly ensued with recovery in several seconds. There were no convulsions. Slight dizziness was noted for several minutes after return of consciousness but this disappeared spontaneously. The blood pressure dropped to 80 mm Hg systolic and 60 mm diastolic.

The patient was then given 0.86 mg of atropine sulfate subcutaneously and the procedure repeated five minutes later. Stimulation of the right carotid sinus produced practically no effect (figure 1d) whereas left carotid pressure produced sinus standstill for only 3.1 seconds after pressure for 10 seconds. The return to normal rhythm was almost immediate after compression was removed (figure 1e). No adverse symptoms were noted with right carotid sinus pressure and only slight dizziness with left carotid sinus pressure. There was no noticeable change in blood pressure in either case after the atropine injection.

Comment This is a case of carotid sinus hypersensitivity in an individual with regular sinus rhythm. The induction of complete cardiac standstill by carotid sinus stimulation is the response usually obtained by virtue of specific or preponderant stimulation of the vagal terminals in the sinoauricular node. In this instance there were no essential differences in the effect of right or left carotid sinus stimulation, except that prolonged pressure on the left carotid sinus after atropinization was still slightly effective. The gastrointestinal symptoms which dominated the clinical picture may be interpreted as vagotonic abdominal effects. This viewpoint has been elaborated by Weiss et al.² Stern⁴ has recently reported a similar case of carotid sinus hypersensitivity in which abdominal manifestations were pronounced. He believed that the disturbances of the bowel were due to severe widespread autonomic discharge involving the afferent limb of the reflex arc in the carotid sinus. It is obvious that in cases such as these in which gastrointestinal manifestations are most prominent, attention might readily be misdirected to the gastrointestinal tract in the search for the correct diagnosis.

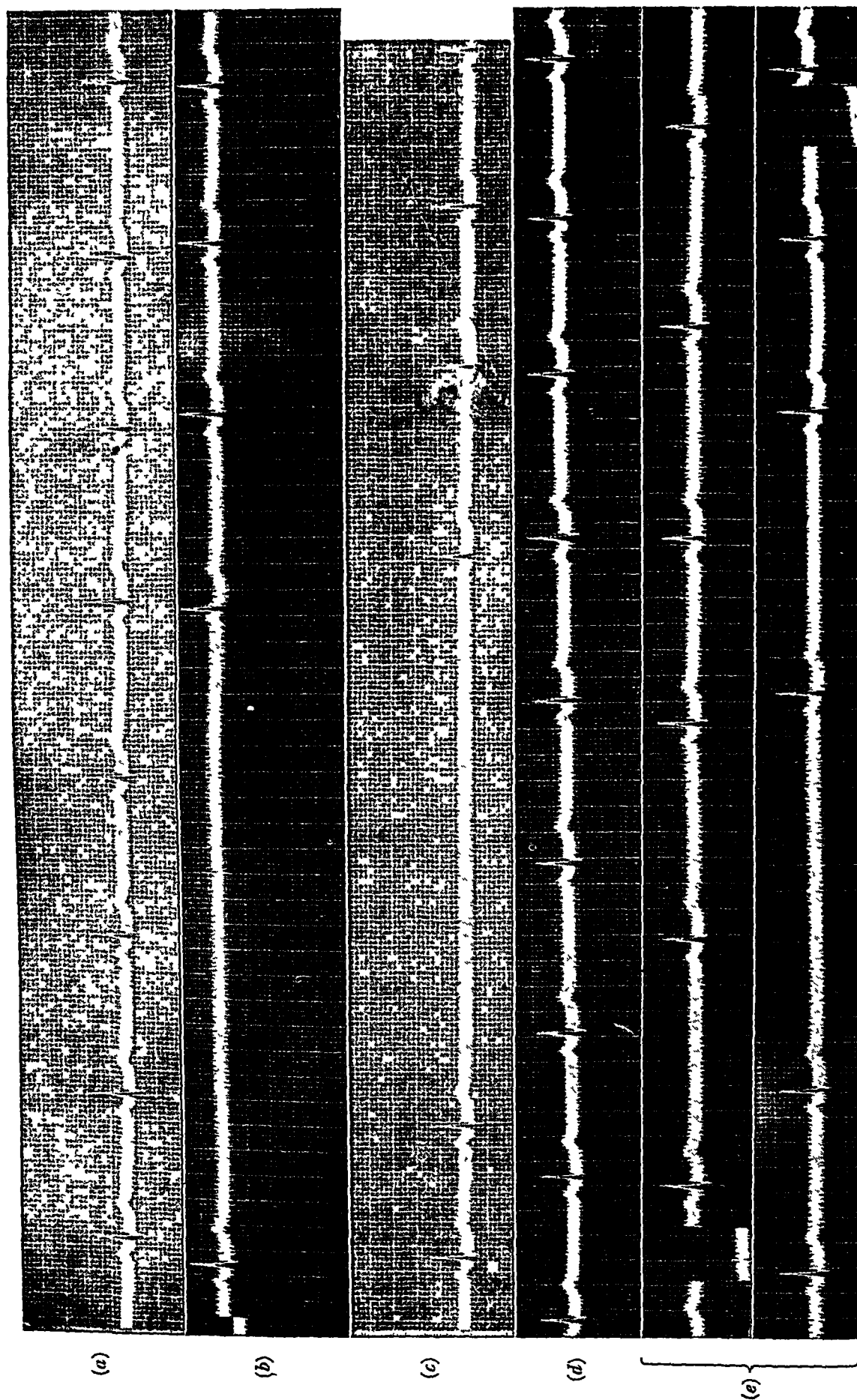


Fig 1 (a) Normal electrocardiogram (b) Illustrates sino-auricular standstill of 5.2 seconds following right carotid sinus pressure The initial beat of recovery is nodal in origin (c) Sino-auricular standstill of 4 seconds following left carotid sinus stimulation (d) Illustrates no effect of right carotid sinus stimulation 5 minutes after administration of 0.86 mg atropine sulfate (e) Left carotid sinus stimulation after administration of 0.86 mg atropine sulfate Illustrates sino-auricular slowing up to 31 seconds

Case 2 A nine-year-old girl was admitted to the New York Post-Graduate Hospital on April 1, 1940. She had been discharged from this hospital three months before, at which time she had been treated for chorea. No cardiac lesion was demonstrable then. She now complained of vague joint pains and fever which varied from 99.8° to 101° F. Physical examination showed that the heart was slightly enlarged, and murmurs indicative of mitral stenosis, mitral insufficiency and aortic insufficiency were present. The pulse rate ranged between 90 and 110. Five days after admission a heart rate of 150 was noted, suggesting the likelihood of paroxysmal tachycardia, particularly since the rate was uninfluenced by mild exertion. This was verified by the electrocardiogram (figure 2a). As far as could be determined, it appeared that the tachycardia had existed for about four hours.

It was decided to try carotid sinus stimulation in an effort to restore the cardiac mechanism to regular sinus rhythm. Figure 2b illustrates the sequence of events when pressure was applied to the carotid sinus. After one second the patient lapsed into unconsciousness and also stopped breathing. As seen in the records, ventricular asystole for 8.4 seconds was produced with evidence of auricular activity continuing during the interval at a rate of 60 to 84 per minute. Auriculo-ventricular conductivity gradually became evident. At first, this was in the form of 2 to 1 block for 5.4 seconds, followed by first grade heart block. The patient was given no stimulation and recovered consciousness shortly after ventricular contractions began. A slight headache was present for several hours after the procedure.

There were several other episodes of paroxysmal tachycardia following this, and momentary carotid sinus stimulation produced similar effects. In this case both right and left carotid sinus pressure were equally effective.

Comment This is a case of paroxysmal tachycardia in which brief carotid sinus stimulation produced ventricular asystole, unconsciousness and respiratory standstill. Regular sinus rhythm then followed with normal auriculo-ventricular conduction after a short period of impaired auriculo-ventricular conduction. The ventricles did not manifest automatic activity at any time. There were no qualitative or quantitative differential effects as regards right or left sided stimulation.

Case 3 A 67-year-old white bookkeeper was first seen in the Out-Patient Department of the New York Post-Graduate Hospital on April 13, 1940. The presenting symptoms were attacks of dizziness and light-headedness of one year's duration. One week previous to admission, he had gone to the New York World's Fair and while looking up at the trylon he suddenly felt dizzy, fainted and was unconscious for several minutes. There were no residual symptoms following this.

For the past seven or eight months, he noticed that light-headedness and dizziness would follow any attempt to look upward. The patient had diabetes for several years, which first required insulin for control but later diet alone sufficed. He had a traumatic amputation of the third finger of the right hand when 12 years of age, herniorrhaphy at the age of 58, and the removal of a basal cell epithelioma of the right eyelid at the age of 59.

About six months prior to hospitalization, he began to complain of exertional dyspnea and occasional attacks of precordial pain with radiation down both arms. He had never noted ankle edema or cough. For five months he had been taking one and one-half grains of digitalis twice daily.

The family history was non-contributory.

The physical examination showed a well developed, moderately obese male, weighing 88 kilograms. There was marked apprehension. The mouth was edentulous.

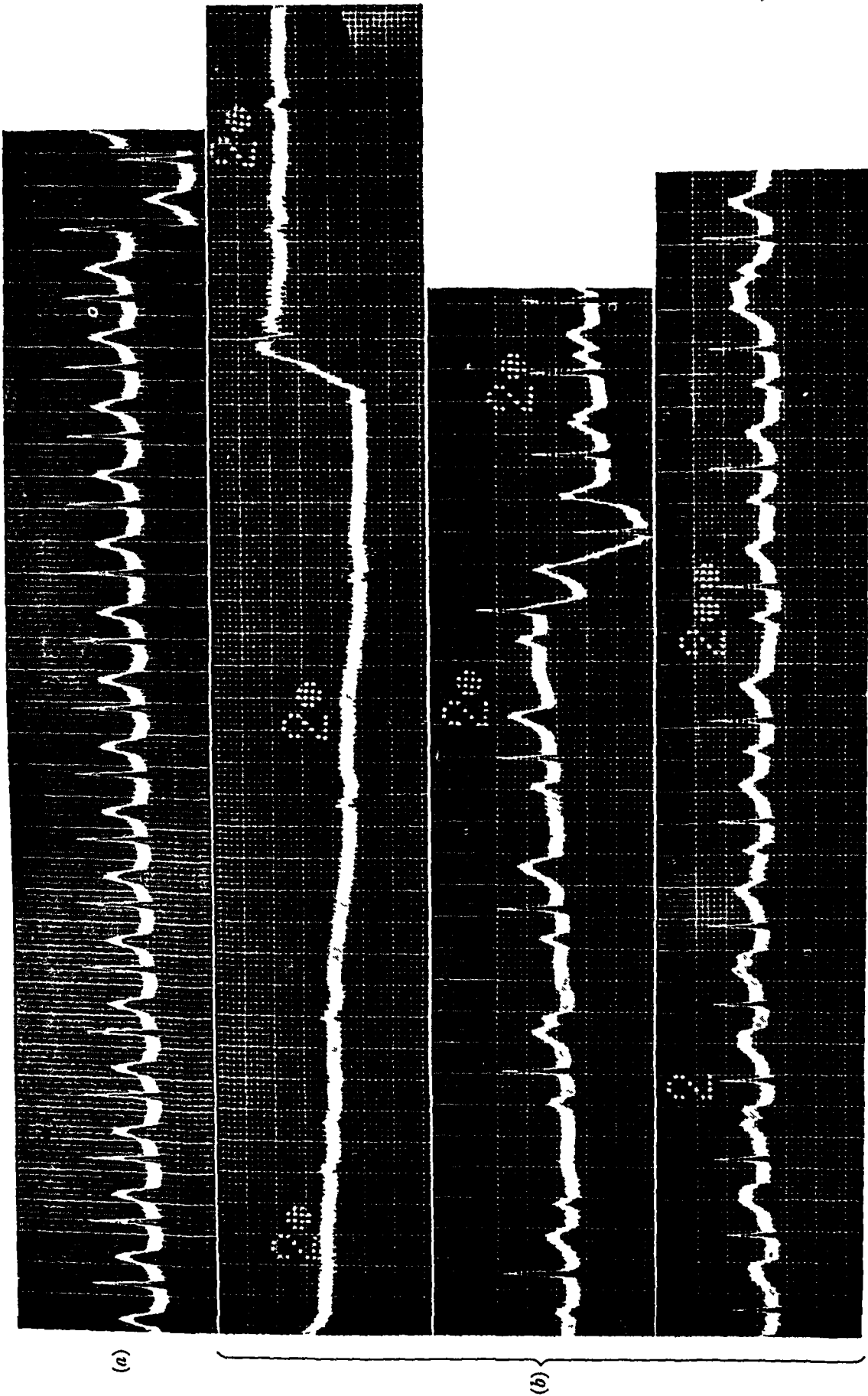


FIG 2 (a) Illustrates paroxysmal auricular tachycardia with ventricular rate of 150 per minute (b) Illustrates sequence of events following carotid sinus stimulation with ventricular asystole of 8.4 seconds Auricular activity continues at rate of 60 to 84 per minute This is followed by 2:1 heart block and finally by first grade heart block

and a slight tremor of the tongue was present. The fundi showed moderate angiosclerosis. No masses were felt in the neck. The thyroid gland was normal. The chest was emphysematous in type. The apex of the heart could not be palpated, percussion revealed the left border of the heart to be 10 cm. from the midsternal line with slight widening of the area of dullness over the aortic area. The sounds were of fairly good quality and no murmurs were heard. The rate was about 68 beats per minute with a completely irregular rhythm. Blood pressure was 150 mm. Hg systolic and 84 mm. diastolic. There were transient basal râles in both lung fields. The liver was palpated at the costal margin. There was slight edema of the lower extremities. The peripheral vessels were moderately sclerotic. The reflexes were physiological.

Laboratory Studies Urinalysis showed 1 per cent sugar and microscopic examination revealed an occasional red blood cell per high power field. The blood count was essentially normal. Wassermann and Kahn tests were negative. The blood sugar (true glucose) was 170 mg. per cent. The electrocardiogram showed auricular fibrillation (figure 3a).

Comment Because of the patient's symptomatology, hyperactivity of the carotid sinus was suspected. The following studies were carried out. Pressure on the right carotid sinus for one second caused complete ventricular asystole for 6.6 seconds. The electrocardiogram showed that auricular activity was not affected and the fibrillary waves continued uninterrupted (figure 3b). The onset of ventricular asystole occurred immediately after pressure was applied. The offset, however, was more gradual with resumption of the original rhythm. Pressure on the left carotid sinus produced essentially the same result except for a slight increase in duration of the ventricular asystole (7.2 seconds) (figure 3c).

In both instances, the patient first complained of dizziness and of a feeling of fullness in the head, this was followed by loss of consciousness. Slight tonic convulsions of the upper extremities were noted which disappeared rapidly as ventricular systole returned. Hyperpnea, pallor of the face and conjugate deviation of the eyes upward and slightly to the left were also noted during the period of asystole and for a short, variable period thereafter.

The patient was then given 0.86 mg. of atropine subcutaneously and after five minutes compression of the carotid sinuses was again applied. As seen in the records, right carotid pressure elicited the same cardiac and peripheral effects as previously noted with ventricular asystole of 7.6 seconds (figure 3d). Left carotid pressure after atropinization, however, produced merely a transient slowing of the ventricular responses (figure 3e) with only slight peripheral effects, namely pallor and dizziness, but no loss of consciousness or convulsions. Apparently in this patient, the right carotid sinus was more sensitive than the left although the effects were evident in the auriculo-ventricular node in both instances.

Case 4 A 47-year-old Italian laborer was referred for an electrocardiogram on April 10, 1940. He had been seen by his physician about four months previously at which time he was in cardiac failure as indicated by dyspnea, orthopnea and peripheral edema. One and one-half grains of digitalis was ordered twice daily. Although he had occasionally been subject to attacks of dizziness, it was only for the preceding two months that these attacks seemed to be more frequent, and at one time he had



FIG 3 (a) Auricular fibrillation with ventricular rate of about 65 per minute (b) Illustrates ventricular asystole for 6.6 seconds following right carotid sinus pressure (c) Auricular waves continued unaffected following left carotid sinus pressure Ventricular asystole for 7.2 seconds (d) Right carotid sinus pressure following administration of 0.86 mg atropine sulfate Ventricular asystole of 7.6 seconds (e) Left carotid sinus pressure following 0.86 mg atropine sulfate, illustrates transient slowing of ventricular response



FIG 4 (a) Illustrates auricular flutter with 2:1 heart block. Ventricular rate 150 beats per minute. Auricular rate 300 beats per minute.
(b) Carotid sinus pressure in auricular flutter. Illustrates ventricular asystole for 3.5 seconds. Auricular impulses continued uninhibited.

actually fainted. The electrocardiogram showed auricular flutter with a 2:1 block, the ventricles beating at a rate of 150 beats per minute and the auricles at 300 beats per minute (figure 4a).

Pressure on the right carotid sinus produced effects particularly on the auriculo-ventricular node with complete ventricular asystole for 3.5 seconds (figure 4b). The auricular impulses continued uninhibited. The patient complained of dizziness, light-headedness and tingling of the fingers and toes. Loss of consciousness did not occur. The patient subsequently volunteered the information that the symptoms produced were almost identical with those he had noted previously, especially since taking digitalis. It was not feasible to repeat the observations on this patient following atropinization.

Comment. This is a case of auricular flutter in which momentary carotid sinus pressure promptly produced ventricular standstill. The promptness of the response and the reminiscence evoked in the patient of previous similar sensations coming on spontaneously seem to justify the case as an instance of carotid sinus sensitivity.

DISCUSSION

The specific physiological alterations which occur in carotid sinus hypersensitivity naturally depend upon whether the cerebral, vasomotor or vagal ("cardiovascular") efferent mechanism is predominantly affected as has so clearly been elucidated by Weiss, Ferris, etc.^{5,6} We have here been concerned only with the cardiac responses. Sigler^{7,8} found that complete cardiac standstill occurred twice as frequently with right as with left carotid sinus pressure whereas high degree auriculo-ventricular block occurred more than twice as frequently with left carotid pressure as with right. Ventricular escape as well as nodal rhythm was occasionally observed. The variations in effect here depend, first, upon individual variations in sensitivity of the right and left carotid sinus, and second upon the nature of the ultimate distribution of vagus fibers to sino-auricular and to auriculo-ventricular nodes.

In general, stimulation of the right carotid sinus particularly affects the sino-auricular node and stimulation of the left carotid sinus principally affects the auriculo-ventricular node, since right vagal terminals are found in greater numbers in the sinus node and left terminals in the auriculo-ventricular nodal area. Both carotid sinuses, however, are represented in the sino-auricular and auriculo-ventricular nodes. The main effects are those of interferences with impulse formation in the sino-auricular node and its subsequent propagation along the auricles and through the conduction system.¹⁰

As far as the differential sinus node and auriculo-ventricular node effects are concerned, the results are completely unpredictable in man and especially so in patients with hyperactive carotid sinus.

If the sinus node is predominantly affected in any given case, sinus bradycardia or sino-auricular standstill will be produced. If the auriculo-ventricular node is predominantly affected, prolonged auriculo-ventricular

conduction of varying grades, up to complete heart block, ventricular escape, or arrhythmias originating below the auriculo-ventricular node may supervene. Premature contractions are also encountered. The ventricular portion of the conduction system is rarely influenced.

We have presented four instances of carotid sinus hypersensitivity occurring in contrasting basic rhythms, namely regular sinus rhythm, paroxysmal auricular tachycardia, auricular fibrillation and auricular flutter.

The three cases of arrhythmia responded to carotid sinus stimulation by ventricular asystole. This was perhaps to be anticipated since the basic rhythms were autonomous as far as the sino-auricular node is concerned and were beyond its influence. The case of regular sinus rhythm responded with complete cardiac standstill, as is frequently observed in this mechanism.

The sensitizing effect of digitalis on the carotid sinus reflex has been emphasized by Weiss, Capps, Munro, Ferris, etc.² and is illustrated by cases 1, 3, and 4. This action probably occurs by virtue of the enhancing effect of digitalis on the vagal efferent portion of the carotid sinus reflex.

This effect should make one circumspect in the administration of digitalis to elderly individuals merely because they have ill-defined symptoms such as fatigue, weakness or dizziness, or as a routine preoperative prophylactic. The argument applies with equal validity to cardiac patients who are about to undergo operations but who are not in demonstrable failure. Case 1 was not in failure when digitalis administration was begun, and although the symptoms antedated the use of the drug, the frequency and severity of the attacks seemed definitely increased after full digitalization.

The gastrointestinal symptoms which are frequently a part of the clinical picture are also illustrated by case 1. This may be interpreted as evidence of vagotonia and the diagnostic difficulties which may ensue have already been commented upon.

The contrasting electrocardiographic effect of carotid sinus pressure in auricular flutter and in paroxysmal tachycardia is worthy of comment, particularly since it is of value in the diagnosis between auricular flutter with 1:1 response and paroxysmal tachycardia. This differentiation is often difficult even with electrocardiographic aid. In auricular flutter, carotid sinus stimulation will impair auriculo-ventricular conduction sometimes up to the point of complete block, depending on individual sensitivity, but the auricular activity will continue uninterrupted. In paroxysmal auricular tachycardia on the other hand, the rhythm, usually, will either be uninfluenced or will revert to regular sinus rhythm.

SUMMARY

1 Four cases of carotid sinus hypersensitivity have been presented, each occurring in a different basic cardiac rhythm, namely regular sinus rhythm, paroxysmal auricular tachycardia, auricular fibrillation and auricular flutter.

2 The results evoked following carotid sinus stimulation on each of

these cases are presented electrocardiographically. The three cases of arrhythmia responded to carotid sinus stimulation by ventricular asystole, whereas the case of regular sinus rhythm responded by complete cardiac standstill.

3 It appears impossible to predict the differential effects of right and left carotid sinus stimulation on the sino-auricular and auriculo-ventricular nodes.

4 Digitalis is shown to exert a sensitizing effect on the carotid sinus reflex, an observation that has previously been made.

5 Gastrointestinal symptoms in patients with carotid sinus hypersensitivity may present diagnostic difficulties.

6 The differential diagnosis between auricular flutter and paroxysmal tachycardia may occasionally be made by studying the electrocardiographic effects of carotid sinus stimulation.

Thanks are due to Miss Marcella Hughes for her technical assistance.

REFERENCES

- 1 WEISS, S, and BAKER, J P. The carotid sinus reflex in health and disease, its role in the causation of fainting and convulsions, *Medicine*, 1933, xii, 297.
- 2 WEISS, S, CAPPS, R B, FERRIS, E B, and MUNRO, D. Syncope and convulsions due to hyperactive carotid sinus reflex, *Arch Int Med*, 1936, lvi, 407.
- 3 HIATT, N, and ADAMS, D. Hyperactive carotid sinus mechanism in auricular flutter, a case report, *ANN INT MED*, 1940, xiii, 1489.
- 4 STERN, J E. Abdominal manifestations from hypersensitive reflexes, *Jr Am Med Assoc*, 1938, cx, 1986.
- 5 WEISS, S. Regulation and disturbance of cerebral circulation through extra-cerebral mechanisms, *A, Research Nerv and Ment Dis, Proc* (1937), 1938, xviii, 571.
- 6 WEISS, S, and BAKER, J P. Dizziness, fainting and convulsions due to hypersensitivity of carotid sinus reflex, *Proc Soc Exper Biol and Med*, 1933, xxx, 614.
- 7 SIGLER, L H. Electrocardiographic observations on the carotid sinus reflex, *Am Heart Jr*, 1934, ix, 782.
- 8 SIGLER, L H. Further observations on the carotid sinus reflex, *ANN INT MED*, 1936, ix, 1380.
- 9 SIGLER, L H. Clinical observations on the carotid sinus reflex, *Am J Med Sci*, 1933, clxxxvi, 118.
- 10 PURKS, W K. Electrocardiographic findings following carotid sinus stimulation, *ANN INT MED*, 1939, xiii, 270.

THE IRON CONTENT OF THE SKIN IN HEMOCHROMATOSIS *

By HAROLD J MAGNUSON, M D , and B O RAULSTON, M D , F A C P ,
Los Angeles, California

QUANTITATIVE estimations of the iron content of skin taken from patients who have hemochromatosis have been and are exceedingly rare Sheldon¹ in his review of world literature in 1935 was able to find only two such analyses, and the results of these were at great variance with each other Muir and Shaw Dunn² found an iron content of 0.188 per cent of the dry weight of the skin, while Loeper, Ravier, and Lesure³ reported 1.15 per cent of the dry weight as iron In view of these discrepancies the following report is considered to be of sufficient interest and importance to justify publication

During the past year we have made spectrographic estimations of the iron content of the skin from 15 patients, some of the specimens being obtained post mortem and some by biopsy In many instances a clinical diagnosis of possible hemochromatosis had been made by reason of two or more of the classical symptoms and signs, namely, diabetes, pigmentation of the skin, and cirrhosis of the liver In three instances the iron content of the skin was increased by as much as five to ten times the value we have obtained in "normal skin" That these three patients represent examples of hemochromatosis has not been proved beyond dispute, but the evidence in favor of such a diagnosis is presented in the summaries of their histories and physical findings This paper is, therefore, presented not as a final, but as a preliminary report in the hope that others will be stimulated to make similar determinations The incidence of hemochromatosis is such that any one group of observers may see but few examples

Method Specimens were obtained either by biopsy under local anesthesia or at autopsy Biopsy specimens should weigh in excess of 200 mg The specimen was carefully washed in distilled water to remove all blood, blotted, and then weighed The sample was then digested in a mixture of concentrated sulfuric and nitric acid For a biopsy specimen of 200 mg, 0.5 cc of concentrated sulfuric acid and 1.0 cc of concentrated nitric acid were used After being taken to dryness, the ash was dissolved in 1 cc of the following mixture Li_2HPO_4 2.0 gm, $\text{Cr}_2(\text{SO}_4)_3$ 20 mg, concentrated HNO_3 10 cc, and water to 100 cc By means of a fine pipette three drops of this solution were then placed on each of nine crater-shaped graphite electrodes which had previously been cleaned by the method of Cholak and Story⁴ The electrodes were kept in an electric oven at 120° C during the

* Received for publication October 28, 1940

From the Department of Medicine, University of Southern California School of Medicine, and the Los Angeles County Hospital

time the solution was placed on them and each drop was allowed to dry before the succeeding drop was added. The specimens were then ailed in an Applied Research Laboratories spectriograph, using a 70 volt direct current with 7.5 amperes across the arc and an arc gap of 10 mm. Three exposures were taken, using three superimposed arcings for each exposure and using a step sector during the exposure. The films were read with a photoelectric densitometer measuring the densities of the chromium line at 2835 \AA and the iron line at 3020 \AA . Readings were also taken from the step sector divisions for the calculation of the gamma of the film. On the basis of the gamma curve the relative intensities of the iron and chromium lines were calculated and by comparing the value of this intensity with those obtained by the addition of known amounts of iron to tissue, the amount of iron in the specimen could be calculated. A blank determination was done in each case, and this value was subtracted from the value obtained for the specimen.

Results

Case	Clinical Diagnosis	Specimens Obtained at	Iron in mg /100 gm Tissue
C S	Hemochromatosis	Biopsy	9.8
L S	"	"	9.8
H F	"	"	9.9
A1	Arteriosclerotic heart disease	Autopsy	1.5
A2	" " "	"	1.2
A3	" " "	"	1.3
A4	" " "	"	1.4
J	Hemochromatosis	Biopsy	5.0
S A	"	"	3.5
R S	"	"	4.4
T G	"	"	3.2
X X	Scleroderma	"	0.5
B S	Hemochromatosis	"	1.9
R	Lymphoma small intestine	Autopsy	2.3
H C	Hemochromatosis	Biopsy	0.75

The iron content of normal skin obtained at autopsy was found by Hoisteis⁵ to be 1.05 mg/100 gm of tissue. Our values taken from autopsy specimens agree fairly well with this value. Specimens taken by biopsy tend to run a little higher, due probably to the fact that not all of the blood could be removed. The first three values given above are greatly elevated and were obtained from patients who were considered to have a correct diagnosis of hemochromatosis. Abstracts of their histories are as follows:

CASE REPORTS

Case 1 H F, a white male, plumber by occupation, was seen at the Los Angeles County Hospital on numerous occasions since 1935 for the control of his diabetes. He was 56 years of age at the time of his first admission. In 1926, when he was 47 years of age, his wife first noted that his hands, forearms, face, neck, and the lower part of his legs presented an unusually deep brown appearance, as though they were

severely tanned This pigmentation started slowly and gradually increased in the areas described In 1934 he developed polyuria, polydipsia, and polyphagia, and experienced a concomitant weight loss of 32 pounds (150–118 pounds) during a period of five months In 1935 because of the above symptoms and severe pruritus he was admitted to the Los Angeles County Hospital for the first time

Of considerable interest was his past history From the age of 15 years the patient had been a plumber and during the first 15 to 20 years of the period he had worked with copper almost exclusively, lining brewery barrels and fitting taps with copper The tubes and pipes were made of copper, and the joints were made of lead Also of interest is the statement that he began to drink whiskey and beer in large quantities at the age of 14 years and continued this practice until he was 39, when one of the results of his entry into the army during the war was curtailment of his drinking At the peak of his drinking experience he was consuming about a quart and a half of whiskey and an occasional drink of beer each day Between the ages of 39 and 56 years his consumption of alcohol was said to have been limited to two or three glasses of beer each week

The patient stated that he had had gonorrhea at the age of 15 and "too many times since to remember" Some time between 1915 and 1925 he is supposed to have had a chancre, which was followed by a positive Wassermann reaction and a course of 20 "lup shots" What medication he received is not known, but he had no further treatment Wassermann and Kahn tests on each admission to this hospital were negative

At the time of his first admission in 1935 diabetes mellitus was diagnosed which was finally controlled by taking a diet of 100 gm each of carbohydrate, fat and protein and 15 units of insulin in the morning and in the evening At this time the pigmentation in the areas described above, and an enlarged liver palpable 5 cm below the costal margin, with a smooth, hard and slightly tender edge, were noted Examination of the blood at this time revealed hemoglobin 94 per cent, erythrocytes 3,350,000, color index 1.34—hyperchromic anemia Leukocytes numbered 7,150 and in the stained smear appeared to be normal Wassermann and Kahn tests were negative

Between 1935 and 1939 he was admitted to the hospital on five different occasions for control of the diabetes During these admissions the following observations were made glucose tolerance curves (following ingestion of 50 gm of glucose) April 30, 1935, fasting sugar 145 mg/100 c.c. blood, one hour after glucose 227 mg/100, two hours, 302 mg/100, three hours, 280 mg/100 c.c., January 28, 1936, fasting 250 mg/100, one hour, 400 mg/100, two hours, 465 mg/100, three hours, 417 mg/100 Skin biopsy December 30, 1937 was found to contain a considerable amount of pigment in the basal cell layer of the epidermis Sections stained for iron revealed a considerable amount of hemosiderin scattered throughout the cutis

In September, 1939, the patient was readmitted because of extreme weakness The additional history obtained at this time revealed that during the past five years he had been impotent and had lost his chest and pubic hair Examination revealed a well-developed and fairly well-nourished man, 60 years of age who was most remarkable because of the pigmentation of his forearms, hands, face and neck, legs and feet The skin over these areas was very dry, smooth, and of deep tan color, which color in reflected light took a somewhat grayer metallic appearance No abnormal pigmentation was present over the trunk or in the mucous membranes The chest and pubes were without hair Blood pressure was 110 mm Hg systolic and 78 mm diastolic The liver was palpable 12 cm below the xiphoid in the midline and had a smooth, sharp, non-tender edge There was no fluid wave, nor were there dilated abdominal veins No other physical abnormalities were found The following laboratory examinations were made Urine (voided) specific gravity 1.010 Protein 1+ Sugar and acetone, none Microscopic examination showed 4 white blood cells

per low power field, occasional hyaline cast Blood Count Hemoglobin 80 per cent, erythrocytes 3,460,000, color index 1.16, leukocytes 5,250, 58 per cent neutrophils, 37 per cent lymphocytes, 3 per cent monocytes, 1 per cent eosinophiles, and 1 per cent basophiles In the stained smear the leukocytes appeared to be normal, the red cells slightly larger than normal and well filled with hemoglobin Icterus index 10 Blood amylase 49 mg produced by 100 cc of serum (normal 70-200) Blood cholesterol 208 mg per cent Serum protein 5.6 per cent albumin 3.3 and globulin 2.3 Glucose tolerance test revealed a fasting level of 192 mg per cent, and levels of 241, 333, and 333, respectively, at one, two, and three hours after ingestion of 50 gm of glucose

Basal metabolic rate was minus 16 per cent Electrocardiogram indicated left axis deviation, low voltage, and sinus arrhythmia Hormone assay of a 48 hour urine specimen revealed no rat units of estriol (normal 0-10) and no capon units (normal 30-45) of androsterone

Microscopic examination of skin removed by biopsy revealed subepithelial iron deposits, by spectrographic estimation the iron content was found to be 9.9 mg/100 gm of tissue

Following discharge on October 11, 1939, the patient was well maintained on a diet of 1700 calories, containing 175 gm of carbohydrate, 70 gm of protein, and 80 gm of fat, and 20 units each of regular and protamine insulin in the morning, and 20 units of regular insulin at night

Case 2 C S, a 52 year old white male, entered the Santa Fe Hospital on April 14, 1940, as a patient of Dr A M Hoffman He had been well until about 18 months before entry, when he first noticed that he became tired more easily than usual This fatigue was not excessive until four months before entry During the three months prior to entry he had noted polyuria and nocturia and for one month had noted an excessive appetite During the four months prior to entry he had lost 10 pounds in weight (196-186) He had not noticed any abnormal pigmentation of the skin

Past history was not significant save that in January, 1939, he had had "pneumonia of the left lung" Several urine examinations by his local physician revealed no sugar at that time

Inventory by systems revealed no additional information

On physical examination the patient was found to be well-developed and well-nourished and to have a marked grayish pigmentation of the hands, face, and feet No pigmentation of the mucous membranes was noted Blood pressure was 130 mm Hg systolic and 80 mm diastolic He was 5 feet 9 inches in height and weighed 186 pounds Aside from the pigmentation mentioned above no abnormalities were noted on physical examination The liver and spleen were not palpable, the abdominal veins were not dilated, and no indications of ascites were present

Results of urinalysis on entry were sp gr 1.032, clear, amber, acid, sugar 3+ (orange), albumin, acetone, and diacetic acid absent Sediment was normal except for a few pus cells Fasting blood sugar was 265 mg per cent when he was on a diet of 150 gm carbohydrates, 80 gm of protein, and 100 gm of fat A 24 hour specimen of urine, totaling 4,000 cc, was found to contain 1.4 per cent, or 56 grams of sugar He continued to excrete between 50 and 110 gm of sugar per 24 hours on the above diet, without insulin

Results of blood count made on admission were Hemoglobin 100 per cent (Sahli), red blood cells 5,000,000, white blood cells 3,800, polynuclear neutrophils 38 per cent, lymphocytes 55 per cent, eosinophiles 5 per cent, monocytes 2 per cent Blood Wassermann reaction was negative

Skin biopsy from the thigh, April 18, 1940, was examined by Dr E M Butt whose report is as follows "The epidermis is normal in appearance In the papillary portion of the corium a few round cells are found Special iron stains reveal the presence of a very small amount of blue staining granular material about some of the

coiled glands A small amount of intercellular pigment is found in the basal layers of the stratum Malpighii This pigment, however, does not stain blue, but is of a light green color This is in all probability iron pigment Diagnosis hemochromatosis" Spectrographic analysis of an adjacent specimen of skin revealed 9.8 mg of iron per 100 gm of tissue

Upper gastrointestinal series revealed no abnormalities

The diabetes proved rather difficult to control because of severe reactions to regular and zinc protamine insulin Positive skin reactions were obtained with zinc protamine insulin and regular insulin The patient was not sensitive to crystalline insulin and was finally stabilized with no urinary sugar and a fasting blood sugar of 165 mg per cent, on a diet of 135 gm carbohydrate, 75 gm protein, 100 gm fat and 350 units of zinc crystalline insulin at 7:30 a m He was discharged May 11, 1940, on above management

Case 3 H F, a white male of 60 years, a painter by trade, entered the Los Angeles County General Hospital in September, 1939, because of amnesia of 48 hours' duration This was apparently due to an acute alcoholic episode When his attention was called to the peculiar color of his skin the patient recalled that it had been dark since he had been in India 40 years before, but that during the four years before entry the pigmentation of the skin of his face, neck, hands and arms had increased He gave no other complaints aside from slight anorexia Past and family history were not significant On examination he was fairly well-developed and nourished and appeared to be somewhat younger than his stated age The skin over his entire body, but especially over the exposed areas of the face, neck, hands, and arms had a blue-gray metallic hue His blood pressure was 140 mm Hg systolic and 100 mm diastolic The heart rhythm was typical of auricular fibrillation, the rate 80 per minute The heart was slightly enlarged to percussion, but no murmurs were heard

Auscultation and percussion revealed no abnormalities of the chest There was no venous engorgement The liver was palpable three cm below the costal margin, was smooth and not tender No other abnormalities were noted

Roentgen-ray examination of the chest, including fluoroscopy, revealed a fibrillating heart moderately enlarged in all diameters A few poorly defined strand-like shadows were seen in each pulmonary apex suggestive of minimal fibrotic tuberculosis without evidence of present activity Roentgen-ray examination of the gastrointestinal tract following a barium meal revealed no abnormalities Gastric juice contained free hydrochloric acid and there was a normal response to histamine In electrocardiograms the T-waves in the classical leads were inverted and auricular fibrillation was indicated Blood Wassermann and Kahn reactions were negative Results of examination of the urine were normal Tests for melanin were negative

Examination of the blood revealed hemoglobin 108 per cent, 5,110,000 erythrocytes, 9,450 leukocytes, 59 per cent polynuclear neutrophils, 27.5 per cent lymphocytes, 5.5 per cent monocytes, 6 per cent eosinophiles, and 2 per cent basophiles Total serum protein was 6.9 per cent, serum calcium 10.4 mg per cent, and serum sodium 318 mg per cent Fasting blood sugar level was 154 mg/100 c c Glucose tolerance test in June, 1940 revealed a fasting blood sugar of 121 mg, one hour—238, two hours—222, and three hours—141 mg per cent No sugar was found in the urine during the test

Skin biopsy from the right forearm was taken for histological and spectrographic examination The sections revealed large amounts of intradermal pigment which did not take stain typical for tissues containing an excess of iron, but gave a strongly positive test for melanin By spectrographic examination, however, the tissue was found to contain 9.8 mg of iron per 100 gm of tissue

In the interval between September, 1939, and June, 1940, the patient had developed signs of congestive heart failure and was digitalized

Comment We are quite certain that the first patient had hemochromatosis. The diabetes, enlarged nodular liver, and typical pigmentation together with the histological demonstration of hemosiderin in skin biopsies on two separate occasions present a rather convincing picture. The second patient, although not showing evidence of cirrhosis, did have the diabetes and the pigmentation. It is true that hemosiderin in the skin on microscopic examination does not warrant the clinical diagnosis of hemochromatosis unless the blood dyscrasias, stasis dermatitis, trauma, and Schamberg's pigmentary dystrophy are ruled out. However, none of these conditions was felt to be present in these patients.

The third patient, on the other hand, presents many problems and possibilities for speculation. It is certain at the outset that this patient does not represent a classical example of hemochromatosis. He had no diabetes, glucose was never found in his urine. On the other hand he did have an elevated fasting blood sugar and a prolonged, though not marked, rise in blood sugar during his glucose tolerance test. It is possible that this behavior of the blood sugar might be due to liver damage. In view of the later development of signs of congestive heart failure one might suggest that the enlargement of the liver was an early manifestation of right heart failure, though at no time was there evidence of increased venous pressure or peripheral edema.

The outstanding problem is the pigmentation. Because of the demonstration of melanin as the pigment one immediately must consider Addison's disease. The elevated blood pressure, elevated blood sugar and glucose tolerance curves, the normal serum sodium, and the general well-being of the patient would appear to rule this out.

Because of the high iron content of the skin, as demonstrated by spectrographic analysis, a content that was nearly identical with that found in the two patients in which the clinical evidence in favor of hemochromatosis was very convincing, we felt that a diagnosis of hemochromatosis must be considered in the third patient. The absence of hemosiderin in the stained sections of the skin certainly does not rule out hemochromatosis. Sheldon¹ reports that in 235 case reports pigmentation was absent in 38 or 16.2 per cent. Johns⁷ recently published the record of a patient who was found to have hemochromatosis, proved at autopsy, whose skin contained no hemosiderin deposits.

That there should be an increase in the iron content of the skin and no demonstrable iron in this tissue by the conventional staining methods is most remarkable. This situation recalls the experience of Sheldon who found in one patient who had hemochromatosis an increase in the iron content of the brain to two and one half times the normal value without a deposit of hemosiderin as indicated by staining methods. Sheldon suggested that this might be due to an increase in the "physiological" iron not accessible to the ordinary staining methods.

ADDENDUM

After this paper had been submitted for publication, patient 1, H F, died, and the diagnosis of hemochromatosis was confirmed at autopsy. The iron content of the skin at autopsy was determined by the o-phenanthroline method described by Hummell and Willard (Ind and Eng Chem, Anal Ed, 1938, x, 13). A value of 75 mg of iron/100 gm of tissue was obtained. Since the iron content of biopsy specimens has been higher than autopsy specimens, this value was felt to be consistent with the 99 mg value reported above in which a totally different method was used. The pituitary was found to contain large amounts of iron, 225 mg/100 gm of tissue. This is of interest in connection with the endocrine abnormalities reported in the history.

ACKNOWLEDGMENT

The authors wish to acknowledge the assistance of Dr A M Hoffman and Dr E M Butt who brought the second case to their attention.

BIBLIOGRAPHY

- 1 SHELDON, J H Haemochromatosis, 1935, Oxford University Press, London
- 2 MUIR, R, and SHAW DUNN, J The iron content of the organs in bronzed diabetes, Jr Path and Bact, 1914, xix, 226-238
- 3 LOEPER, M, RAVIER, J, and LESURE, A Les deux pigments du diabète bronze, Progres med, 1928, lv, 1461-1462
- 4 CHOLAK, J, and STORY, R V Spectroscopic analysis of biological material, Ind and Eng Chem, 1938, x, 619-622
- 5 HORSTERS, HANS Über den Eisengehalt der Organe bei Ikterus, Arch f exper Path u Pharmacol, 1930, clii, 198-209
- 6 MONTGOMERY, H, and O'LEARY, PAUL A Pigmentation of the skin in Addison's disease, acanthosis nigricans, and haemochromatosis, Arch Dermat and Syph, 1930, xxi, 970-984
- 7 JOHNS, H J Haemochromatosis without pigmentation of the skin resistance to protamine zinc insulin, Jr Am Med Assoc, 1939, cxlii, 2272-2273

MENINGOCOCCAL MENINGITIS

REPORT OF FIFTY CASES, FORTY TREATED WITH SERUM AND TEN TREATED WITH SERUM AND SULFANILAMIDE *

By EUGENE P CAMPBELL, M D , *Philadelphia, Pennsylvania*

DURING the past decade we have witnessed important changes in the therapeutic regimen of meningococcal meningitis. The traditional method of administering serum intrathecally has been generally discontinued in favor of the intravenous route. New and improved methods of making serum have resulted in the introduction of highly concentrated antiserum and antitoxin. Supporters of serum and antitoxin using new methods of administration of these biological preparations have claimed promising results. It almost goes without saying, however, that the general fatality from this disease has remained high in spite of these innovations. It is for the purpose of critical analysis of a relatively small amount of experience with another therapeutic agent (sulfanilamide) that this report is made.

From a historical point of view many other chemicals have been used in the treatment of meningococcal meningitis. Several of them have been very popular, but during the early part of the last decade the effectiveness of immunobiological methods almost completely overshadowed all other methods of treatment. In 1936 the principle of chemotherapy was again revived by the introduction of sulfanilamide. Since then sulfanilamide and sulfapyridine have both been widely used in the treatment of meningococcal infections. Comprehensive reviews of the pharmacotherapeutic actions of these drugs have been published by many authors ^{1, 2, 3, 4}

The present report is a study of 50 cases of meningococcal meningitis occurring during a four year period ending May 1939. With the exception of one case, they all were treated at the Philadelphia General Hospital. Studies of the mode of onset, symptoms and physical findings are not within the scope of this paper. These features have been thoroughly analyzed in more comprehensive monographs.

This collection of 50 cases was made up of two relatively homogeneous groups. Forty of the patients were treated with serum while the remaining 10 were treated with both serum and sulfanilamide. Age, sex, and race distributions are indicated in table 1. The most serious obstacle to this statistical analysis came about when an attempt was made to evaluate the effect of a possible change in the severity of the disease during the second half of this four year period as compared with the first half. Inasmuch as the case fatality rate for a 40 year period in Philadelphia (chart 1) has been rather

* Received for publication June 14, 1941

From the Medical Service of the Philadelphia General Hospital, under the directorship of Dr. Russell S. Boles

TABLE I

Selected Clinical and Laboratory Features Occurring in 50 Cases of Meningococcal Meningitis

	Serum Treated	Serum Sulfanilamide	Total Cases	
1 Sex				7 Cells in spinal fluid Average no in 41 cases—9,243
Male	28 (4)*	7	35	
Female	12 (1)*	3	15	
2 Race				8 Average amount of serum by route
White	29 (3)*	4	33	Intrathecal 58 0 c c
Negro	11 (2)*	6	17	Intravenous 58 7 c c
3 Age groups				Intramuscular 30 7 c c
0-4	2	2	4	Total average 108 8 c c
5-9	4 (2)*	2	6	9 Total amount of sulfanilamide given to 6 patients = 10-25 grams
10-19	6	4	10	
20-29	11	1	12	10 Classification of cases by severity
30-39	7 (1)*		7	Mild 4
40-49	7 (1)*	1	8	Ordinary type 12
50-59	2		2	Severe 29
60-69	1 (1)*		1	Fulminating 5
4 Rash				11 Outcome for whole group
Petechial	12 (3)*	5	17	Recovered 30
Purpuric	2 (1)*		2	Died 20
5 Meningococci recovered from spinal fluid	37 (5)*	10	47	(Autopsies 16)
6 Blood cultures				
Positive	2	2	4	
Negative	13	6	19	

* Fulminating cases

constant, it is assumed that no unusual change in severity of the disease occurred during the time of the present study. The meningococci recovered from our patients were not typed so it is not known whether the less virulent Group II^a was more or less prevalent during the latter half of this period. It is recognized that certain unavoidable elements of non-homogeneity were present. For example, no single physician had immediate charge of the treatment of all of the patients, thus allowing certain personal differences in methods to influence the outcome. The general scheme of treatment with serum in vogue during this four year period consisted of intraspinal, intravenous and intramuscular doses of a potent antimeningococcal serum in daily or semidaily doses. During the last two years sulfanilamide was added to the regimen.

The type and potency of the serum and its route of administration were essentially the same in both groups. Practically all of the serum used was of the highly concentrated type, 10 c c of which represented 30 c c of the unconcentrated variety. The average total amount of serum given to each patient in the serum group was 108 c c. In the serum-plus-sulfanilamide

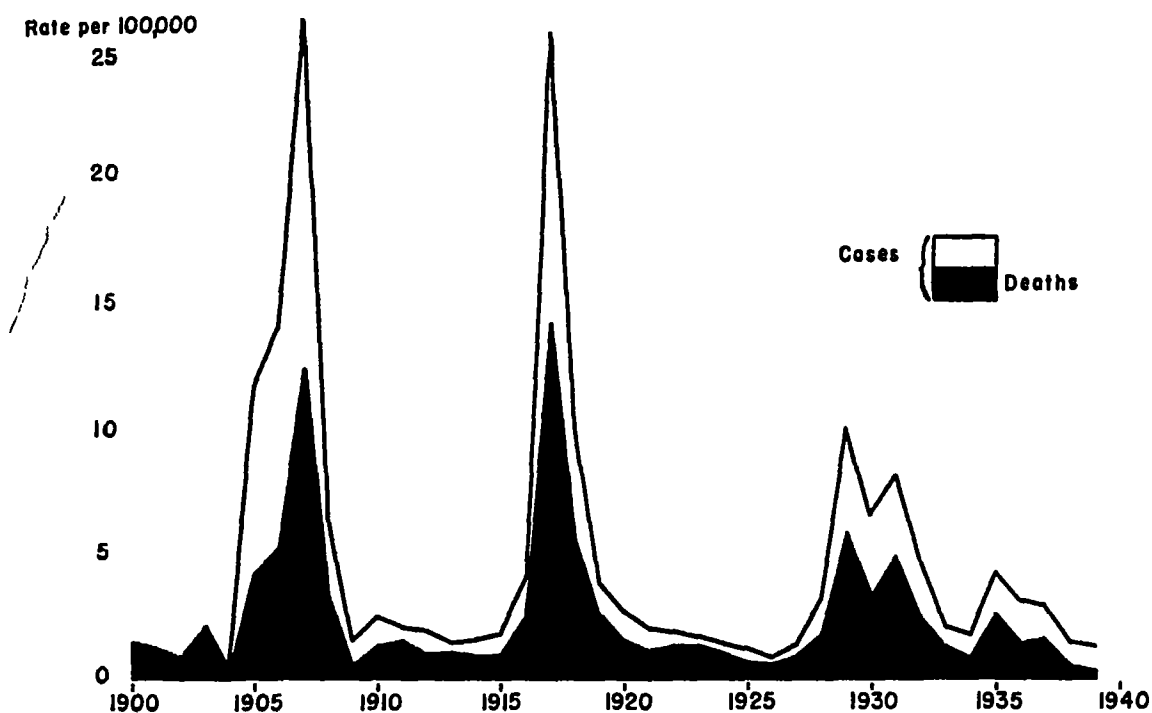


CHART I Case rates and death rates from meningococcal meningitis in Philadelphia, 1900-1940

group an average of 109 c c was given per patient. One patient was given 20,000 units of antitoxin in addition to 25 c c of concentrated antiserum. Sterile air was introduced into the spinal canal of a few patients. Improvement could not be directly attributed to this procedure. A summary of certain clinical and laboratory features of the 50 cases is presented in table 1.

A classification of the cases by severity, as suggested by Herrick, reveals the rather important fact that of the 50 cases, five were of the fulminating type (10 per cent) and all of these were in the serum group. Four of the fulminating cases died within 24 hours of admission. The fifth was in the hospital less than 36 hours, but treatment was delayed because the diagnosis was obscured by acute alcoholism. Compared to another group study,⁶ I feel that the high fatality in the group herein reported is accounted for in some measure by the relatively larger proportion of severe and fulminating cases. Inasmuch as all of the fulminating cases occurred in the serum treated group it was considered advisable to classify them separately in order to make the two treatment groups more nearly comparable (table 2).

Table 3 lists the incidence of complications that occurred in the 50 cases. It is notable that deafness, at one time a much more common complication, occurred only once in this series. Jaundice developed in one patient following the administration of sulfanilamide; it was mild and disappeared when the drug was discontinued. The only other complication directly attributable to the sulfanilamide was vomiting, which occurred in the same patient presenting the jaundice. One of the four patients who developed bronchopneumonia died.

TABLE II

Results of Treatment of 50 Cases of Inter-epidemic Meningococcal Meningitis

Method of Treatment	Cases	Deaths	Fatality
1 Serum alone	35	15	42.8%
2 Serum and sulfanilamide	10	0	0
3 Fulminating cases* (4 died in less than 24 hours)	5	5	100.0%
Total	50	20	40.0%

* Fulminating cases were separated because adequate treatment was not possible before death and also because no fulminating cases occurred in the serum and sulfanilamide treated group

The four patients presenting signs and symptoms suggestive of meningococcemia comprise the mild group. The most outstanding characteristic of the condition in these four patients was the prolonged period of illness before admission to the hospital. In these patients the condition existed 14, 21, 35, and 42 days respectively before entrance to the hospital (average 28 days). In 41 of the other patients giving a reliable history, the average duration of illness before hospitalization was 3.1 days (range one to eight days). In addition, the septicemic stage of these four patients was characterized by intermittent fever, arthralgia, rash, headache, chills and sweats. All four of

TABLE III

Incidence of Various Complications Occurring in 50 Cases of Meningococcal Meningitis

	Cases		Cases
Bronchopneumonia	4	Pyelitis (<i>B. coli</i>)	1
Meningococcemia	4	Deafness, partial	1
Otitis media	2	Myositis, lumbar muscles	1
Adenitis	2	Sinusitis	1
Jaundice	2	Alcoholism, acute	1
Interstitial keratitis	1	Chronic meningitis	1
Vomiting	1		

the patients developed meningitis⁷ presumably as a result of chronic meningococcal septicemia. Three of the patients recovered promptly following the administration of small doses of antimeningococcal serum. The fourth recovered after treatment with serum and sulfanilamide.

In this era of intense interest in medical therapy there are certain features of meningococcal infections that are often overlooked. Seldom does one find reports of multiple cases occurring in families or in the same house. Few reports give the incidence of recurring attacks in the same person. It is from a careful study of these features of the disease in conjunction with specific group identification of the invading meningococcus that important epidemiologic and immunologic problems concerning meningococcal meningitis may be solved. The number of multiple cases discovered in this small

group is astonishingly high One family of three members all developed meningitis within one month (table,4a) The father became ill 28 days after the onset of the same disease in his daughter and 26 days after the onset in his wife He died after an illness of less than three days' duration Neither the daughter nor the wife had been discharged from the hospital before the father became ill A second group of three cases occurred in a building that housed two negro families (table 4b) Three children contracted the

TABLE IV
Multiple Cases in a White Family (a) and the Same House (b) Occurring in a Group of 50 Cases of Meningococcal Meningitis

Name	Age	Sex	Race	Date of Onset	Date Adm to Hospital	Outcome
(a) 1 E W	12	F	W (Daughter)	3/22/36	3/26/36	Recovered
2 L W	30	F	W (Mother)	3/24/36	3/27/36	Recovered
3 W W	35	M	W (Father)	4/19/36	4/21/36	Died
(b) 1 H K	5	M	C	5/1/37	5/4/37	Died
2 L K	2	M	C	5/5/37	5/6/37	Recovered
3 G W	9	F	C	5/8/37	5/9/37	Died

disease within a week Two died, one 12 hours after admission to the hospital In 46 families represented in this group two had three cases each (4 per cent) It should be noted that for the purposes of this study the one house in which two negro families lived is considered one family unit

There is little uniformity of opinion regarding the incidence of second attacks of meningococcal meningitis Stallybrass in 1931⁸ states "second attacks are almost unknown" On this basis he believes that the immunity is of "high degree" Others⁹ report rare instances of second attacks In

TABLE V
Recurring Attacks in Three Patients

Name	Age	Sex	Race	First Attack	Second Attack	Outcome
1 F M *	28	M	C	6/20/35	1/16/36	Recovered
2 J D *	28	M	W	7/28/35	11/14/35	Recovered
3 G D *	19	M	W	5/7/36	5/21/38	Recovered

* Both attacks of F M and J D and the second attack of G D were treated at the Philadelphia General Hospital

this group of 50 cases of meningococcal meningitis 48 persons are represented and in these 48 patients three had second attacks (table 5) Such a high incidence of second attacks would seem to indicate that the degree of immunity is not very durable

The duration of hospitalization is of practical importance In these two groups the average period of hospitalization for 20 serum treated patients (recovered) was 36 3 days In the serum plus sulfanilamide treated group

the average period was 26.7 days. This is a saving of nearly 10 days per patient.

Much is being written concerning the efficacy of the various chemotherapeutic agents in the treatment of meningococcal meningitis as compared to antiserum. From a statistical standpoint the results of treatment in the two groups represented in this study may be stated as follows. Assuming there is no difference in the results of treatment by these two methods and assuming the true proportion of deaths is 15 in 35 (42.8 per cent), then the probability of obtaining no deaths in 10 cases taken at random is one in 269. Under these conditions, then, it is fair to say that there is slight probability of having 10 cases with no deaths. Since the addition of sulfanilamide is the one important difference between these two groups, I feel that it is safe to conclude that sulfanilamide produced a significant reduction in the fatality.

The studies made of the use of sulfapyridine and sulfathiazole, though meager in number, have also been very encouraging. The collected results of seven different methods of treating 2,747 cases of meningococcal meningitis are summarized in table 6. The limitations of such an accumulation of

TABLE VI

Results of Treatment of 2,747 Cases of Meningococcal Meningitis by Different Methods
(Collected from the Literature August 1937 to January 1941)*

Method of Treatment	Cases	Deaths	Fatality per cent
1 Sulfadiazine (alone)	13	1	7.6
2 Sulfathiazole (alone)	70	3	4.3
3 Sulfapyridine (alone)	588	23	3.9
4 Sulfanilamide and sulfapyridine (combined)	214	17	7.9
5 Sulfanilamide (alone)	588	66	11.2
6 Serum and sulfanilamide	165	20	12.1
7 Serum (alone)	1,109	349	31.4
Total	2,747	478	

* The bibliographic references to this table will be supplied on request.

figures are threefold. The usual differences between one author and another in the management of cases of meningitis is not a serious one but is probably more important during interepidemic times. Several instances of small groups of cases (2-10 cases) were included in the table. A third and serious limitation is the fact, emphasized by Branham,⁵ that during interepidemic times the less virulent Group II meningococcus predominates as the cause of meningococcal meningitis, whereas during epidemic times Group I predominates. Consequently, even though the conclusion seems valid that chemotherapy is the best method to use in treating this disease, and despite the fact that this prediction may be made for epidemic times as a result of interepidemic studies, one is by no means justified in supposing that this conclusion has been adequately proved.

SUMMARY

1 Among 40 patients treated with serum there were 20 deaths (included among the deaths were five fulminating infections) In 10 patients treated with serum and sulfanilamide there were no deaths

2 The incidence of certain features such as multiple cases, recurring attacks and meningococcemia, as they occurred in this group of patients, is given Important epidemiologic and immunologic information may be obtained from a study of these features of this disease

3 From the results of this study as well as the reports of others it seems clear that chemotherapy alone or in combination with immune serum is the most effective way of treating meningococcal meningitis

BIBLIOGRAPHY

- 1 WHITBY, LIONEL Chemotherapy of bacterial infection, Lancet, 1938, ii, 1095-1103
- 2 LONG, P H, and BLISS, ELEANOR A The clinical and experimental use of sulfapyridine and allied compounds, 1939, Macmillan Co, New York
- 3 FLIPPIN, HARRISON F, SCHWARTZ, LEON, and ROSE, S BRANDT The comparative effectiveness and toxicity of sulfathiazole and sulfapyridine in pneumococcic pneumonia, ANN INT MED, 1940, xiii, 2038-2049
- 4 BRANHAM, S E The effect of sulfapyridine and sulfanilamide with and without serum in experimental meningococcus infection, Pub Health Rep, 1937, lii, 1143-1150
- 5 BRANHAM, S E The meningococcus (*Neisseria intracellulalis*), Bact Rev, 1940, iv, 59-96
- 6 CAMPBELL, E P Meningococcal meningitis, Med Ann District of Columbia, 1939, viii, 132-135
- 7 CARBONELL, A, and CAMPBELL, E P Prolonged meningococcemia, Arch Int Med, 1938, lxi, 646-654
- 8 STALLIBRASS, C O The principles of epidemiology and the process of infection, 1931, Macmillan Co, New York, p 276
- 9 SHAFFER, H W, and FREEMAN, J T Epidemic meningitis, second attack with recovery, 2 cases, Jr Lab and Clin Med, 1937, xlii, 1010-1013

FATIGUE OF PATIENTS WITH CIRCULATORY INSUFFICIENCY, INVESTIGATED BY MEANS OF THE FUSION FREQUENCY OF FLICKER *

By NORBERT ENZER, M D , F A C P , ERNST SIMONSON, M D , and
SAMUEL S BLANKSTEIN, M D , *Milwaukee, Wisconsin*

PATIENTS with circulatory insufficiency from heart disease and hypertension fatigue easily, not only in heavy or moderate muscular work, but also in types of light muscular work, in mental work and even in resting condition. This cannot be explained by the circulatory insufficiency alone, the increase of the oxygen consumption during those types of work is very slight, and these patients are still able to increase the cardiac minute volume more than would be necessary to cover the slightly increased demands for oxygen consumption and transportation.

This question has some practical significance. There are several million cardiac patients with slight symptoms of decompensation, who are able to perform some occupational work with slight muscular effort, and who are in fact employed at such occupations as typing, office work, shop work, secretarial work, etc., where the general fatigue is due to the fatigue of the central nervous system. It is well known that the central nervous system is especially sensitive to lack of oxygen (Heymans,¹ Simpson and Derbyshire,² Sugar and Gerard³). The literature in regard to the effects of cerebral anemia are given in the reviews of Wolff⁴ and of Quastal.⁵ We believe that the state of the central nervous system is an essential factor in the increased fatigability of patients with heart disease or hypertension.

We (Simonson and Enzer⁶) found decrease of the fusion frequency of flicker in normal subjects after fatigue in types of work with prevailing fatigue of the central nervous system. The fusion frequency is considered to be one of the most fundamental of visual functions (Crozier⁷ and Hecht⁸). The fusion frequency of flicker is that rate of successive stimuli which is just necessary to produce complete fusion and has the same effect as continuous illumination (Duke-Elder⁹). A diminution of the fusion frequency in patients would mean that the circulatory insufficiency has produced a similar or even more manifest state of fatigue than the usual occupational work in normal subjects. It would mean, at the same time, a decreased resistance of the central nervous system of patients with circulatory insufficiency against fatigue in types of work requiring only slight muscular effect. It appears to be possible to use the fusion frequency of flicker to

* Received for publication February 8, 1941
From the Research Laboratory of the Mount Sinai Hospital, Milwaukee, Wisconsin

judge the capacity of patients for those types of work. This is important because no other method hitherto described is suitable for this purpose. We have combined our cases of cardiac diseases and hypertension into one group, because the effect on the central nervous system is quite similar. In heart disease there is a *general* deficiency of oxygen supply, in hypertension this is due to a local vascular disturbance but often combined with a general insufficiency. The patients either were compensated or exhibited some decompensation symptoms of different degree, but none of them was bedridden.

METHOD

We used a rotator arrangement where the beam of light from an electric bulb (25 watt Mazda) is interrupted by a rotating disk with various openings. The light was projected onto an opal glass to obtain proper diffusion. The speed of the rotator could be easily and minutely varied by a friction screw and was measured by a mechanical revolution counter and a stop watch. The disk used had four identical openings equally spaced with a relationship of the openings (flashes) to the dark intervals of 64:36 (= 64 per cent). The subject was seated with his head placed on a chin rest so that the distance from the illuminated area to the eye was kept constantly at one meter. The illumination of the surroundings was kept constant with a vertical intensity of illumination at the plane of the illuminated area, facing the patient, of 20 foot-candles, and a vertical intensity of illumination at the subject's face, facing the machine, of 0.32 foot-candles. The illumination of the area was turned on and off by means of an electrical throw switch. The time of exposure was limited to 1.5 seconds which is the physiological optimum (Riddell¹⁰). The size of the illuminated area was 100 sq mm subtending a visual angle of one-half degree. Consequently, all of our results concerned the fovea exclusively. Binocular central fixation was used. The illumination was kept constant by means of a voltage regulator and reduced by a diaphragm to 0.0033 candle power per sq cm.

Under these standard conditions 47 normal subjects and 22 patients with (primary or secondary) heart diseases and hypertension in different states of compensation were investigated. The vision of the 47 normals and 19 of the patients was normal or corrected to normal values with glasses. In three of the patients the vision was reduced to between 15/170 to 15/50 (cases 14, 19, and 21).

The results were checked by repeated testing. With only very few exceptions, the difference between the repeated tests was very small. The deviation of the values, when repeated during one testing, did not exceed, as a rule, 1 to 1.5 flashes. The daily variations were somewhat greater, but did not exceed, as a rule, three flashes provided that the general condition of the subject was the same. Also, in our former investigations on the effect of

fatigue in the fusion frequency of flicker,⁶ we found only small daily variations. Interference by colds may greatly alter the values obtained.

Although the method is a subjective one, it has many characteristics of an objective method. The subject does not know the significance of detecting the flicker nor the actual speed of the rotator. The fact that our values coincide so closely on repeated testing, indicating an exact end point, excludes any effort on the part of the patient to influence the results. The investigation of the fusion frequency of flicker can be regarded as an excellent method for clinical investigations because it is rapid and accurate. The subject only indicates the presence or absence of flicker.

The description of our pathological cases is summarized in table 1.

TABLE I

No	Age	Sex	Description of Patients
1	28	F	Fully compensated mitral stenosis
2	17	F	Compensated mitral stenosis, complicated by pregnancy
3	54	F	Hypertension 215/140. Dyspnea, headache, occasional precordial pains. E K G reveals myocardial damage. Advanced arteriosclerosis of retinal vessels.
4	59	F	Hypertension 170/100. Occasional severe dyspnea, heart enlarged to left.
5	72	M	Hypertension 230/140. No symptoms of cardiovascular decompensation.
6	53	F	Hypertension 170/100. Occasional pain in chest. Moderate arteriosclerosis of retinal vessels.
7	33	F	Rheumatic heart disease. Repeated decompensation and digitalization.
8	52	M	Compensated mitral stenosis.
9	66	M	Coronary occlusion. E K G. Myocardial damage. Occasional precordial pain. Dyspnea on exertion. Obesity.
10	62	M	Auricular fibrillations and coronary occlusion. No cardiac enlargement.
11	73	M	Chronic glomerulonephritis and amyloidosis. Left hydrothorax. Some peripheral edema. N P N 78.2 mg per cent. Cardiac hypertrophy.
12	65	M	E K G shows moderate myocardial damage, premature ventricular contractions. Peculiar sound at mitral area suggests calcification of valve. Moderate cardiac hypertrophy. Recurrent attacks of syncope.
13	65	M	Arteriosclerotic heart disease, with cardiac decompensation, peripheral edema, dyspnea, palpable liver, cardiac enlargement. Reduced kidney function. E K G reveals auricular fibrillations, and myocardial damage. Blood pressure 160/100.
14	53	M	Mitral stenosis. Symptoms of decompensation (repeated unconsciousness) in history, moderate cyanosis.
15	60	M	Hypertensive heart disease, taboparesis. Blood pressure 220/130. Cardiac enlargement, dyspnea, rapid pulse.
16	41	M	Pulmonary emboli with severe pulmonary infarction 18 months previously. Occasional dizziness, dyspnea on exertion. Fatigability. No objective cardiovascular findings. E K G shows low voltage and tendency to right axis deviation.
17	21	F	Hyperthyroidism and hypertension, 169/100. B M R +37%. No symptoms of decompensation.
18	65	F	Pernicious anemia. 3.8 million erythrocytes, hemoglobin 78 per cent. Fatigues easily.
19	63	M	Coronary occlusion. E K G confirms infarct. Angina pectoris, advanced arteriosclerosis of retinal vessels with hemorrhages.
20	30	M	Hypertension 150/120. Headaches. Fatigability. No symptoms of decompensation.
21	45	F	Essential hypertension 220/100. No symptoms of decompensation.
22	24	F	Hypertension and cardiac decompensation due to chronic glomerulonephritis.

RESULTS

We found a clear cut influence of age on the fusion frequency¹³, this began definitely after the age of 30, the values of older subjects did not exceed a fusion frequency of 45 flashes per second, but younger subjects may show as low values as those of older people. The lowest normal value of 47 normal subjects was 40.2 flashes per second, the mean value for all age groups was 44.9.

We do not know the actual values of the fusion frequency of our patients before the development of their disease state. Thus, we are not able to ascertain the correct decrease of the fusion frequency. We can conclude only that there is a pathological decrease, if the value is lower than the lowest normal value obtained in a sufficiently large number of controls. But this does not exclude a pathological decrease in any case in which the values are somewhat higher than the lowest values.

Only two values were found to lie between the normal average (*A*) and the lowest normal limit (*L*) (table 2). One was observed in a patient with

TABLE II
Fusion Frequency of Flicker in Patients with Circulatory Insufficiency

Case No	Flashes per sec
A = Normal Average = 44.9	
1	44.0
2	41.6
L = Lowest Normal Limit = 40.2	
3	31.4
4	35.6
5	37.8
6	36.0
7	34.0
8	37.0
9	35.0
10	32.5
11	39.0
12	40.0
13	34.8
14	32.6
15	37.6
16	39.1
17	38.8
18	33.0
19	30.8
20	36.0
21	36.0
22	34.8

fully compensated mitral stenosis, who felt very well on the day of investigation and during the following four months that she was observed. The other, also, was found in a patient with compensated mitral stenosis, complicated, however, by four months' pregnancy at the time of first examination. As this patient was very young, it is quite possible that the findings indicated a considerable decrease of fusion frequency. A second examination of this

patient was performed three months after the first examination. The values were identical within the experimental error: first examination, 41.6, second examination, 41.2.

All other 20 values are below the lowest normal limit, i.e., they must be regarded as pathologically decreased. The mean value of the groups with circulatory diseases is remarkably lower than that of the normal group. The mean value of all normal subjects is 44.9, that of all 22 patients is 36.1 in which the high values of two perfectly compensated patients are included, although these cases may be regarded as normal with respect to subjective symptoms, actual working capacity, and clinical data. The flicker at a speed of 36.2 flashes per second is easily manifest to the normal subjects. Thus, in all clinical cases the fusion frequency is markedly decreased. This must be attributed to an oxygen lack in the visual pathway as a whole resulting from the circulatory insufficiency.

No parallelism was found between the height of the blood pressure and the decrease in the fusion frequency in the cases with an uncomplicated hypertension but with normal vision.

We found that cases of hypertension, when complicated by general circulatory decompensation (cases 4, 13 and 22), show distinctly lower values of fusion frequency than cases of hypertension without clinical circulatory disturbances (cases 5, 15, 17 and 20). Three cases of hypertension showed advanced arteriosclerotic changes of the retinal vessels (cases 3, 6 and 19). No decompensation was present in case 6, but in cases 3 and 19 there were some symptoms of decompensation. The fusion values were all lower than could be explained by the hypertension alone or the findings of some decompensation symptoms. We feel that the presence of advanced retinal arteriosclerosis indicates a more severe local vascular involvement of visual pathways as a whole and explains the comparatively lower values.

Riddell¹⁰ believes that a lowered visual acuity in otherwise normal subjects decreases the fusion frequency. We found, however, in some preliminary experiments that this finding cannot be generalized because some forms of lowered vision are not accompanied by decrease of the fusion frequency. This is to be a subject for a later communication.

Consequently, we believe that the factors mentioned above are more significant in reducing the fusion frequency than the lowered visual acuity found in cases 14, 19 and 21.

Cases 11, 12 and 16 with no hypertension, but with some cardiac involvement, and some slight symptoms of cardiac decompensation, showed only a slight decrease in the fusion frequency. When more cardiac involvement is present, as in cases 7, 14 and 22, without hypertension, the fusion frequency is significantly lower.

The analysis of the material shows that there is undoubtedly a relationship between the value of the fusion frequency and the actual state of the patient. The worse the condition of a patient, the lower was the value of fusion frequency.

The method will give even better results when used repeatedly on the same patient. In patient 10 we found a fusion frequency of 32.5 in our first investigation. With the improvement in his general condition, after an interval of eight weeks, the fusion frequency was likewise increased to 35.6, but still pathologically decreased. The following experiment is a further illustration of the importance of the general status for the fusion frequency. Shortly after obtaining a fusion frequency of 37.6 on patient 15, he was subjected to the mild exertion of the finger ergograph. During this performance he suffered a slight collapse without unconsciousness. After 15 minutes of recovery the fusion frequency obtained was 35.2 and on rechecking the same value was obtained. This reduction is quite significant since it exceeds the experimental error by 100 per cent.

DISCUSSION

In local or general circulatory insufficiency there is an anoxemia of the tissues including the brain (Altschule,¹¹ Wiggers¹²). Our data are further strong evidence of the importance of an adequate oxygen supply for the proper function of the visual pathway.

If this view is correct other pathological types of insufficient oxygen supply should show a decrease of the fusion frequency. We investigated a patient (No. 18) with pernicious anemia and found a fusion frequency of 33.0. In this case the lack of oxygen supply is not due to mechanical insufficiency of the circulatory system but to the diminished oxygen content of the arterial blood. The effect, however, in regard to the fusion frequency is the same. This experiment indicates that it is the lack of oxygen to the central nervous system and retina which is responsible for decreasing the fusion frequency in heart diseases and hypertension.

Thus, the decrease of the fusion frequency in circulatory insufficiency shows the deterioration of an important sensory function, which to a certain degree is an indication of the state of the whole nervous system. Our results may also be regarded as suggesting the physiological background for the increased fatigue in types of work with prevailing fatigue of the central nervous system and with only slight muscular effort. The fusion frequency of patients with *slight* decompensation symptoms during rest is as low as in some normal subjects in the state of pronounced fatigue, and in patients with *moderate* symptoms of decompensation (such as dyspnea on exertion, some edema in the evening, some cardiac enlargement, etc.) it is even lower.

SUMMARY

- 1 The fusion frequency of flicker has been investigated in 22 patients with hypertension and heart disease.

- 2 With the exception of two fully compensated cases of mitral stenosis, all values of the patients are lower than the lowest normal values observed in 47 normal subjects.

3 The decrease of fusion frequency throws additional light on the actual state of the patient

4 The decrease of fusion frequency is directly concerned with the oxygen supply to the visual pathway as a whole

5 The decrease of the fusion frequency indicates a certain permanent degree of fatigue of the central nervous system and explains also the decreased working capacity of patients with circulatory impairment in types of work with slight or no muscular effort

BIBLIOGRAPHY

- 1 HFMANS, C, BOUCKAERT, I I, JOURDAN, F, NOWAK, I G, and FARBER, S Survival and revival of nerve centers following acute anemia, *Arch Neurol*, 1937, xxxviii, 304
- 2 SIMPSON, H N, and DERBYSHIRE, A J Electrical activity of the motor cortex during cerebral anemia, *Am Jr Physiol*, 1934, cix, 99
- 3 SUGAR, O, and GERARD, R W Anoxia and brain potentials, *Jr Neurophysiol*, 1938, i, 558
- 4 WOLFF, H G The cerebral circulation, *Physiol Rev*, 1936, xvi, 545
- 5 QUESTAL, E G Respiration in the central nervous system, *Physiol Rev*, 1939, xix, 135
- 6 SIMONSON, E, and ENZER, N Measurement of fusion frequency of flicker as a test for fatigue of the central nervous system, *Jr Indust Hyg*, 1941, xxiii, 83-89
- 7 CROZIER, W J On the sensory discrimination of intensities, *Proc Nation Acad Sci*, 1936, xii, 412
- 8 HECHT, S The nature of the visual process, *Bull New York Acad Med*, 1938, xiv, 21
- 9 DUKE-ELDER, W Textbook of ophthalmology, 1932, C V Mosby Co, St Louis, Vol I, p 459
- 10 RIDDELL, A L Use of flicker phenomenon in investigation of field of vision, *Brit Jr Ophth*, 1936, xx, 385
- 11 ALTSCHULE, M D Chronic cardiac decompensation, *Medicine*, 1938, xvii, 75
- 12 WIGGERS, C J Physiologic meaning of common clinical signs and symptoms in cardiovascular disease, *Jr Am Med Assoc*, 1931, xcvi, 603
- 13 SIMONSON, E, ENZER, N, and BLANKSTEIN, S The influence of age on the fusion frequency of flicker, *Ji Exper Psychol*, 1941, xxix, 252

SULFONAMIDES: PASSAGE INTO SPINAL FLUID AND RECTAL ABSORPTION *

By WINDSOR C CUTTING, M D , and ERNEST H SULTAN, A B ,
San Francisco, California

THE increasing importance of sulfathiazole in the treatment of bacterial infections makes it desirable to elucidate any differences from the more familiar sulfanilamide, particularly concerning distribution in the body. Thus it has been thought that sulfathiazole penetrated into the spinal fluid less readily than sulfanilamide, and was also less readily absorbed from the rectum. This report presents results on these aspects of the sulfonamides in animals and patients.

SPINAL FLUID PENETRATION

Sadusk and coauthors,¹ in 1940, claimed that spinal fluid concentrations of sulfathiazole, from 0 to 25 per cent of the simultaneous blood values, occurred after four hours of administration of the drug, and from 10 to 20 per cent of the blood levels after 24 hours. Carey² reported similar low concentrations as compared with the much higher penetration previously reported by Marshall and coworkers for sulfanilamide.³ We have compared the blood and spinal fluid levels of sulfanilamide, sulfapyridine, and sulfathiazole in dogs and patients.

Dogs Two unanesthetized dogs were given the drugs either orally or rectally, the usual dose being 0.15 gm per kilo body weight. Simultaneous blood and spinal fluid estimations of the drug were made at intervals from four to 24 hours after administration. No local anesthetic was used for the spinal punctures. Nine comparisons with sulfanilamide were made: the blood concentrations varied from 1.1 mg (free) to 14.6 mg per cent (free), with an average spinal fluid concentration of 81 per cent (range, 50 to 100 per cent). The time within the limits of four to 24 hours after drug administration appeared to have no effect on the relative concentrations. Five comparisons with sulfapyridine showed less regularity: spinal fluid concentrations varied from 0 to 100 per cent of the blood level, with blood levels from 0.1 to 5.2 mg per cent. Five comparisons with sulfathiazole showed consistently low spinal fluid concentrations: the spinal fluid level was from 0 to 29 per cent (average 14 per cent) of the blood concentration, except in one trial in which the 24 hour level of spinal fluid sulfathiazole was 250 per cent of the blood level. Thus it would appear that penetration

* Received for publication September 9, 1941.

From the Departments of Pharmacology and of Medicine, Stanford University School of Medicine, San Francisco, California.

Supported, in part, by the Rockefeller Fluid Research Fund of Stanford University School of Medicine.

of sulfathiazole into the spinal fluid is much less than that of sulfanilamide, in dogs. However, a paradoxically high level may be obtained in the spinal fluid, when the blood is nearly cleared of the drug and before it has all escaped from the spinal canal.

Patients Ten comparisons of blood and spinal fluid concentration of sulfathiazole were made in patients without meningitis. With blood concentrations (free) varying from 0.3 mg to 8.3 mg per cent, the spinal fluid concentrations varied from 0 to 44 per cent of the blood level, and averaged 20 per cent.

Meningitis For comparison with these values for patients without meningitis, some observations were made on patients with meningeal infections*. The results are summarized in table 1.

It is seen that spinal fluid penetration of all three of the sulfonamide drugs used was considerable. In contrast to the 20 per cent penetration of sulfathiazole through normal meninges, the average in patients with meningitis was 53 per cent. This was somewhat less than the 82 per cent average for sulfanilamide, and the 89 per cent average for sulfapyridine. However, these percentages must be regarded as indicative of general trends due to the relatively few determinations which could be made. There was no consistent change in spinal fluid penetration of drug as the meningitis subsided in patient 5, or increased in severity in patient 6, in whom it ended fatally.

RECTAL ABSORPTION

Several reporters have claimed that sulfathiazole is poorly absorbed from the rectum, although no satisfactory comparisons of rectal and oral absorption of the different sulfonamide compounds have been made previously. Reinhold and coworkers,⁴ in 1939, were among the first to mention the poor absorption of sulfathiazole. Both Hartmann and coworkers⁵ and Neal and coworkers⁶ have administered sulfapyridine or sodium sulfapyridine by rectum. In one trial, in which the sodium salt was given in 2 per cent solution, the former authors⁵ reported a blood concentration of 4 mg per cent. Local irritation was not mentioned. A more complete study of the absorption of sulfanilamide has been reported by Marino and coworkers,⁷ and particularly Turell.⁸ Marino and coworkers reported that sulfanilamide was absorbed somewhat from suppositories, though more definitely from a 1 per cent solution. Turell claimed that both solution and suppositories were effectively absorbed, repeated dosage resulting in blood concentrations as high as 9 to 11 mg per cent (total). Turell also reported that sulfanilamide was absorbed from an isolated rectal loop in man. We have made further studies in dogs and in patients.

Dogs We administered sulfanilamide, sulfapyridine and sulfathiazole, in turn, to two dogs, both by mouth and by rectum, in doses of 0.15 gm per

* We are grateful to Dr. H. K. Faber, Professor of Pediatrics, Stanford University School of Medicine, for permission to include patients 4, 5, and 6.

TABLE I
Comparative Blood and Spinal Fluid Concentrations of Sulfonamides in Meningitis †

Day	Drug	Drug Concentration		
		Blood, mg per cent	Spinal Fluid, mg per cent	Per Cent Penetration into Spinal Fluid
Patient 1 Pyogenic meningitis				
1	Sulfanilamide started			
7	" "	4 5	4 2	93
7	Sulfapyridine started			
9	" "	6 1	4 4	72
10	Sulfathiazole started			
14	" "	1 7	1 2	71
16	" "	2 7	1 3	47
Patient 2 Pneumococcus meningitis				
1	Sulfapyridine started			
16	" "	6 2	3 7	60
Patient 3 Influenzal meningitis *				
Single dose	Sulfathiazole	2 5	1 6	
Patient 4 Lymphocytic choriomeningitis				
Single dose	Sulfanilamide	8 0	7 6	95
Patient 5 Influenzal meningitis				
1	Sulfanilamide started			
2	" "	14 5	8 5	59
3	" "	8 6	7 2	83
3	Sulfathiazole started			
4	" "	6 8	3 2	47
5	" "	9 1	3 8	42
6	" "	9 3	2 2	23
7	" "	7 3	3 2	44
8	" "	5 5	3 6	65
Patient 6 Influenzal meningitis				
1	Sodium sulfathiazole started			
2	" " "	8 4	4 1	49
3	" " "	6 0	3 0	50
4	" " "	5 3	3 2	60
7	" " "	3 6	3 1	86
8	Sulfanilamide started			
10	" "	3 6	2 8	78
10	Sodium sulfapyridine started			
13	" " "	14 4	7 7	53
14	" " "	13 2	8 6	65
15	" " "	7 8	9 5	122
16	" " "	6 0	4 2	70
16	" " "	14 0	11 5	82
17	" " "	8 4	12 6	150
18	" " "	6 2	5 5	89
19	" " "	5 2	6 5	125

* Spinal fluid estimation was made a few hours later than the blood estimation, dosage constant

† Days in first column of table mean total consecutive days of medication, except where single doses are indicated, and blood and spinal fluid estimations were made on particular days indicated

kilo body weight A total of 16 administrations was given Blood samples, obtained two, four, six, and 24 hours after administration, were analyzed for the drug concentration Figure 1 illustrates the results obtained in dog 1, the results with dog 2 showing roughly the same relationships It is seen that, although all three drugs were quite well absorbed by mouth, only sulfanilamide was absorbed appreciably from the rectum

In these two dogs, the drug was given by rectum as a powder in an open half of a gelatin capsule, and followed by 10 to 20 c c of water through a rubber catheter Since it was assumed that the drug did not ascend farther than the rectum, or lower colon, dog 3 (5 kg) was used to compare rectal absorption with absorption higher in the colon, where large rectal infusions

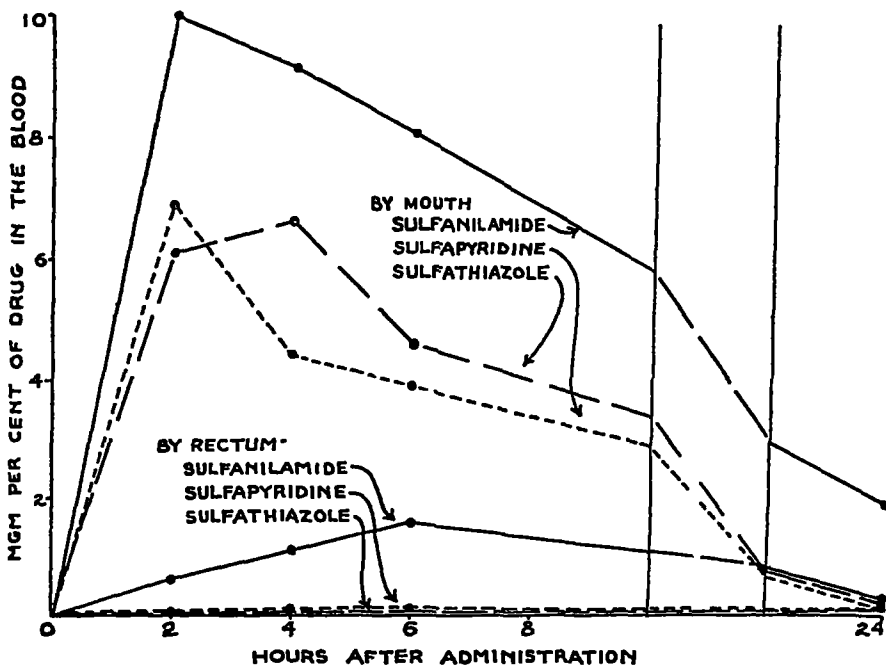


FIG 1 Comparative absorption of sulfonamides by mouth and by rectum in dog 1

of the drug in solution might at times be expected to reach Under sodium pentobarbital anesthesia, the rectum was ligated near the anus, and a ligature was applied at the splenic flexure of the colon Into the segment thus formed, 0.5 gm of sulfanilamide, in 1 per cent solution, was introduced Blood samples were taken every 20 minutes, and at the end of one hour, the blood concentration of sulfanilamide being 4.4 mg per cent The contents of this segment were then removed by thorough washing with normal physiologic salt solution After an interval of two hours, the blood concentration had fallen to 3.4 mg per cent At this time, a new segment reaching from the splenic flexure of the colon to four inches past the ileocecal valve was tied off Into this loop, 0.25 gm of sulfanilamide in 1 per cent solution

was introduced (half the former dose), and blood samples again taken at 30 minute intervals. At the end of one hour, the blood sulfanilamide concentration was 11.3 mg per cent. Accordingly, the absorption from the upper colon was found to be far superior to that from the rectum, half the dose of sulfanilamide giving twice the absorption, as indicated by the blood concentration of the drug.

Patients Observations somewhat similar to those in dogs were made in 16 patients in order to compare rectal absorption of sulfanilamide, sulfapyridine and sulfathiazole. The compounds were administered in 4 gm doses, suspended in 30 to 50 cc of water, being given easily from a triump glass syringe through a larger rubber catheter. Blood was obtained two, four, six, and 24 hours after administration for determination of the drug content. All values reported are for the free forms of the drugs, and are summarized in table 2.

TABLE II
Rectal Absorption of Sulfonamides in Patients

Patient	Body Weight kg	Dose, gm	Blood Concentration (mg per cent)			
			2 hours	4 hours	6 hours	24 hours
Sulfanilamide						
Be	45	4	1.8	2.7	2.7	1.3
VL	75	4	1.8	2.4	2.6	1.7
Sa	81	4	1.8	2.2	2.5	1.4
Ge	69	4	2.3	3.4	3.6	2.0
Ga	82	4	2.6	2.6	2.4	0.7
Sa	81	10	0.6	2.0	2.0	1.0
Ga	65	10	2.8	—	—	0.9
Ya	57	10	2.9	2.7	2.4	0.9
Ph	58	10	3.0	—	—	1.5
Ra	68	10	3.1	—	—	3.5
Ca	58	10	5.0	6.5	6.7	2.2
Sl	58	10	9.4	8.7	11.9	10.8
Sulfapyridine						
Na	74	4	0.1	—	0.1	0
Sm	67	4	0.2	—	0.2	0
Ga	82	4	0.2	0.2	0.3	0.1
Sa	81	4	0.3	0.2	0.2	0
Mo*	64	4	0.6	0.5	0.4	—
Sulfathiazole						
Re	60	4	0	0	0	0
Pa	55	4	0	0	trace	0

* Sodium sulfapyridine

It is clear that sulfapyridine and sulfathiazole were not substantially absorbed from the rectum. In a single trial with a solution of sodium sulfapyridine this was found to be too irritating to be retained more than one-half hour. Sulfanilamide, however, was readily absorbed, the average blood level at six hours, after 4 gm doses, being 2.8 mg per cent, and at 24 hours,

1.4 mg per cent. The rather uniform blood levels reached with 4 gm doses, despite a considerable variation in the weight of the patients, raised a question as to whether the drug was absorbed until a constant blood level was reached, depending on a fixed diffusion gradient from a saturated solution of sulfanilamide. That this was not entirely true was shown by the results following the administration of 10 gm doses. Here, although in certain patients the blood level did not rise higher than with 4 gm doses, in others it rose to rather high levels. According to these results, rectal absorption of sulfanilamide was found to be variable, but in no case did it fail to be absorbed. Even with the smaller doses in large patients, a blood concentration of over 2 mg per cent was present six hours after rectal administration of the drug.

As a further observation on the constancy of rectal absorption, 0.5 gm of sulfanilamide, with 10 c.c. of water, was placed in a dog's rectum (5 kg.), and the anus was closed by suture. It was found that the blood concentration of sulfanilamide rose steadily, until at eight hours it had reached a peak of 4.9 mg per cent, after which it fell gradually until at 27 hours it was 1.9 mg per cent. There was no evidence of a long plateau which could be interpreted as a period when a fixed diffusion gradient was maintaining a constant blood level from a saturated solution in the rectum. This confirmed the observations in patients.

DISCUSSION

That sulfathiazole penetrates into the spinal fluid poorly in normal dogs, and even in patients with meningeal inflammation only about half as well as sulfanilamide, should not be interpreted as indicating that this drug has no place in the treatment of meningitis. If the infecting organisms are decidedly more susceptible to sulfathiazole than to sulfanilamide, as is apparently the case with the staphylococcus, sulfathiazole should be used. In pneumococcus infections, sulfapyridine has about the same effectiveness as sulfathiazole. The former drug, therefore, would appear to be superior in pneumococcus meningitis, owing to its better penetration, unless the greater toxicity of sulfapyridine is a consideration. Occasionally, spinal fluid concentrations were found by us which were higher than the simultaneous blood levels of sulfapyridine and sulfathiazole. This may indicate merely a slow disappearance of these drugs from the spinal fluid, as compared to a more rapid escape from the blood.

The results on rectal absorption indicate that only sulfanilamide has a possible therapeutic value by this route. The rather low blood levels obtained, after single doses, may be increased with repeated administration of large doses, but the rectal route remains a relatively inefficient method of administration. However, this does not mean that it is useless. When vomiting interferes with oral administration, and vigorous therapy is not necessary, the ease with which a nurse can give sulfanilamide by rectum may make it the route of choice. Similarly, postoperatively, if drugs are contra-

indicated by mouth, or in children who resist oral medication, rectal administration might occasionally be useful. Prophylactically, in operations on the rectum, it might also be valuable. The administration of a suspension of the drug has the advantage of simplicity, although greater absorption is to be expected from large volumes of solution, which ascend higher up the colon. Since sulfanilamide settles quickly from suspension the mixture should be vigorously stirred, immediately sucked up into a large syringe and injected at once through a catheter previously inserted into the rectum. The syringe is then removed, partly filled with water, and the drug remaining in the catheter is washed into the rectum.

Although other reporters have described the administration of sulfapyridine rectally, it would appear that repeated, large doses in large volumes of water would be necessary to obtain satisfactory blood concentrations of the drug. Sodium sulfapyridine, however, has been claimed to be satisfactory, although in our single observation, it was too irritating to be retained. If given in a large volume of water, it might have the disadvantage of acting as an enema, unless given very slowly.

Why slight differences in molecular size and constitution so abruptly change the penetrating powers of the sulfonamides through biological membranes is not understood. The superior penetration of sulfanilamide through the meninges and the rectal mucosa is in agreement, however, with its more ready absorption from the upper alimentary tract. Fundamental studies of these interesting differences between the sulfonamides are desirable.

CONCLUSIONS

1 Sulfathiazole, when given by mouth, was found to enter normal spinal fluid to a concentration of only about 20 per cent of the simultaneous blood concentration, roughly twice this concentration would penetrate through inflamed meninges.

2 Sulfapyridine and sulfanilamide penetrated more efficiently into the spinal fluid in meningitis, the concentrations in the spinal fluid approaching the blood levels of these drugs.

3 Rectal absorption of sulfapyridine and sulfathiazole was practically nil in dogs and patients.

4 Rectal absorption of sulfanilamide, although variable, was always considerable, and, when low blood concentrations will suffice, rectal administration may be a valuable method for therapeutic administration of this drug.

REFERENCES

- 1 SADUSK, J. E., ET AL. Observations on absorption, excretion, diffusion and acetylation of sulfathiazole in man, *Yale Jr Biol and Med*, 1940, xii, 681-696.
- 2 CAREY, B. W. Use of sulfanilamide and related compounds in diseases of infancy and childhood, *Jr Am Med Assoc*, 1940, cxv, 924-929.

- 3 MARSHALL, E K, JR, ET AL Para-aminobenzenesulfonamide, J₁ Am Med Assoc, 1937, cviii, 953-957
- 4 REINHOLD, J G, ET AL Observations on pharmacology and toxicology of sulfathiazole in man, Am J_r Med Sci, 1940, cxcix, 393-401
- 5 HARTMANN, A F, ET AL Present status of therapy with sulfanilamide and sulfapyridine, J_r Missouri Med Assoc, 1940, xxxvii, 41-54
- 6 NEAL, J, ET AL Sulfapyridine and its sodium salt in the treatment of meningitis, J_r Am Med Assoc, 1940, cxv, 2055-2058
- 7 MARINO, A, ET AL Rectal administration of sulfanilamide, Med Times, 1940, lxxviii, 110-112
- 8 TURELL, R Absorption of sulfanilamide from the large intestine, Ann Surg, 1940, cxlii, 417-420

STREPTOCOCCAL MENINGITIS

FOUR CASES TREATED WITH SULFONAMIDES IN WHICH THE ETIOLOGICAL AGENT WAS AN UNUSUAL STREPTOCOCCUS

By LOWELL A. RANTZ, M D, *San Francisco, California*

THE meninges, like the synovial membranes and the endocardium, are unique in that they are frequently the site of infections caused by organisms not ordinarily regarded as highly pathogenic for man.

It is, therefore, to be expected that many varieties of streptococci should have been observed to be etiological agents in meningitis. It is apparent that this is so from a survey of reported cases of this disease. From such a study it is difficult to assess the relative frequency of the various types of streptococci in meningitis or to form an accurate estimate of mortality rates for types other than the hemolytic. The Lancefield technic¹ has not been applied in many instances of streptococcal meningitis so that the distribution of Lancefield groups as etiological agents in streptococcal meningitis has not been established.

It is the purpose of this paper to summarize the available information in regard to streptococcal meningitis, particularly in reference to its etiology, mortality under non-specific therapy, and in relationship to the sulfonamide drugs, and to present four cases, all of which received chemotherapy, of streptococcal disease of the meninges caused by unusual streptococci.

INCIDENCE AND PREDISPOSING FACTORS

Streptococci are responsible for approximately 17 per cent of 1566 cases of bacterial meningitis described by Neal². No evidence as to the frequency of hemolytic and non-hemolytic varieties has been presented. In this clinic during the last seven years 36 cases of bacterial meningitis have been observed. Six, or 16 per cent, of these were caused by streptococci, of which five were hemolytic and one non-hemolytic.

Lancefield grouping of hemolytic streptococci derived from cases of meningitis has been applied in only a few instances. The vast majority of such strains have been shown^{3,4} to be members of Group A. Haie¹ mentions three instances of infections due to Group B, but details are entirely lacking. Thomas⁵ has described a case in which "minute" hemolytic streptococci were the etiological agents. These may have been members of Group F⁶. Biological and serological studies have rarely been applied to strains of non-hemolytic streptococci obtained from the meninges.

Thirty-eight per cent of all cases of streptococcal meningitis⁷ are asso-

* Received for publication May 15, 1941.

From the Department of Medicine, Stanford University School of Medicine, San Francisco, California.

ciated with otitis media, 24 per cent follow injuries to or operations upon the skull and spine, 10 per cent follow upper respiratory infections, 5 per cent occur in association with sepsis, 19 per cent are of unknown etiology, and the remainder are associated with a variety of conditions. The hemolytic streptococcus was presumably responsible for most of these infections. Eighteen cases of non-hemolytic streptococcal meningitis have been described^{8, 9, 10} in which it is possible to determine the predisposing factors involved, 22 per cent were associated with otitis media, 44 per cent followed operation or injury, 11 per cent followed upper respiratory infections, and there were 11 per cent in which no evidence of previous disease was obtainable. Trauma to the central nervous system is, therefore, nearly twice as frequently present in these cases as in hemolytic streptococcal disease of the meninges.

MORTALITY AND RESPONSE TO THERAPY

Neal,² from her very large experience, stated in 1938 that the mortality rate of hemolytic streptococcus meningitis was 95 per cent before the introduction of the sulfonamide drugs. Nearly all of these cases were probably caused by streptococci members of the Lancefield Group A. That certain of the recovered cases may not have been, is emphasized by the case of Rosenberg and Nottley⁸ in which the streptococcus isolated from the spinal fluid was described as "partial hemolyticus" and was probably a member of some other group.

With the application of sulfonamide therapy approximately 20 per cent of individuals suffering from hemolytic streptococcal meningitis have died.¹¹

It is very much more difficult to obtain accurate data as to the mortality rate of non-hemolytic streptococcal meningitis. Fifty-nine cases of spontaneous recovery from streptococcal meningitis have been reported^{8, 9, 10} in which the etiological organism has been described in relation to its action upon blood agar. Twenty-seven per cent of these were non-hemolytic or formed green pigment. Since 17 per cent of cases of streptococcal meningitis in this clinic were caused by this type of organism it seems fair to conclude that the mortality rates of meningitis due to hemolytic and non-hemolytic streptococci are approximately the same. Five cases of meningitis due to non-hemolytic streptococci or *Streptococcus viridans* have been described^{10, 12, 13} in which sulfonamides have been used. Four recovered and one died.

Four additional cases in which streptococci other than members of the Lancefield Group A were etiological agents in infections of the meninges will now be described. All received chemotherapy, three recovered and one died. The bacteriology of each is presented, the organisms being classified by the system proposed by Sherman¹⁴ and by the Lancefield technic using precipitating antigens prepared by a modification of the formamide method of Fuller¹⁵ and the micro method of Brown.¹⁶

CASE REPORTS

Case 1—Lancefield Group B Meningitis Mrs A C, a 48-year-old white housewife, entered the hospital January 4, 1941 demonstrating the signs of compression of the spinal cord at the level of the twelfth thoracic vertebra without evidence of other disease. Examination of the blood and urine was not remarkable. Laminectomy was performed on that day and a meningioma was removed. The post-operative course was associated with fever for two days followed by two days of normal temperature. At this time there was a chill, rapid rise in temperature to 39° C, accompanied by the development of headache, stiffness of the neck and malaise. On the following day cisternal puncture was performed and a cloudy spinal fluid obtained which contained 4,000 cells per cubic millimeter all of which were polymorphonuclear. The sugar content was 100 mg per 100 cubic centimeters. Culture of the fluid and of the blood revealed hemolytic streptococci. On the following day sulfapyridine therapy was instituted, 14 grams being administered by mouth over a period of 48 hours. The temperature gradually returned to normal and she made an uneventful recovery, except for the development of a severe facial and oral herpes simplex on the third day after the onset of the meningitis. It should be pointed out, however, that the blood culture was already sterile before the onset of drug therapy, that the temperature was markedly lower, the neck less stiff, and that she was obviously improving.

Bacteriology Hemolytic streptococci were recovered from both the blood and the spinal fluid. In the former instance there was one colony, and in the latter 10 per cubic centimeter. These organisms have been demonstrated by the precipitin reaction to be members of the Lancefield Group B.

Comment This is a case of meningitis following laminectomy in which the etiological agent was a hemolytic streptococcus of the Lancefield Group B. The infection was characterized by a sharp onset with positive blood and spinal fluid cultures and the typical signs of meningitis. The spinal fluid sugar content was normal. Very marked improvement occurred before sulfonamide therapy was begun and the blood culture had become sterile. It is, therefore, unlikely that chemotherapy exercised an especially beneficial effect on the course of events in this case.

Case 2—Enterococcus Meningitis Mr R M, an 18-year-old white male school boy, entered the hospital October 9, 1940 with a complaint of mastoiditis and brain abscess of one month's duration. The family history was noncontributory, as was the past history, except for the fact that he had had a draining right ear for 18 months. The present illness had begun on September 8, 1940, with otalgia and the appearance of a yellow discharge from the ear. The clinical course of the disease is illustrated in figure 1. Four days later his physician performed a right myringotomy. Mastoidectomy was performed 72 hours later because of the development of fever and headache. Granulations on the dura and an epidural abscess were found and drained, but no thrombosis of the lateral sinus was demonstrated. The temperature returned to normal for a brief period, then became markedly elevated and the blood culture was positive for a streptococcus with alpha hemolysis. The mastoid was reexplored and a large abscess of the temporal lobe was exposed and drained. The spinal fluid obtained by lumbar puncture was normal and cultures sterile.

Eight grams of sulfathiazole were administered daily by mouth for 10 days after operation. His temperature returned to normal and he was greatly improved. During this period he received six transfusions of whole blood. Two days after the cessation of the drug the temperature again became elevated, headache and vomiting developed, and he was transferred to the Stanford University Hospitals.

The physical examination revealed a well developed young man who was conscious and well oriented. The temperature was 39° C, the pulse 90, the respirations 22 per minute, and the blood pressure 120 mm Hg systolic and 70 mm diastolic. Examination of the eyes showed that the left pupil was larger than the right but both reacted to light and accommodation, while in the fundus papilledema of 3 diopters was observed. The brain was found to be herniating into the right mastoid wound. The mouth and nasopharynx were normal and the neck was slightly stiff, the heart, lungs and abdomen were not remarkable. The extremities showed no abnormalities and the neurological examination was within normal limits.

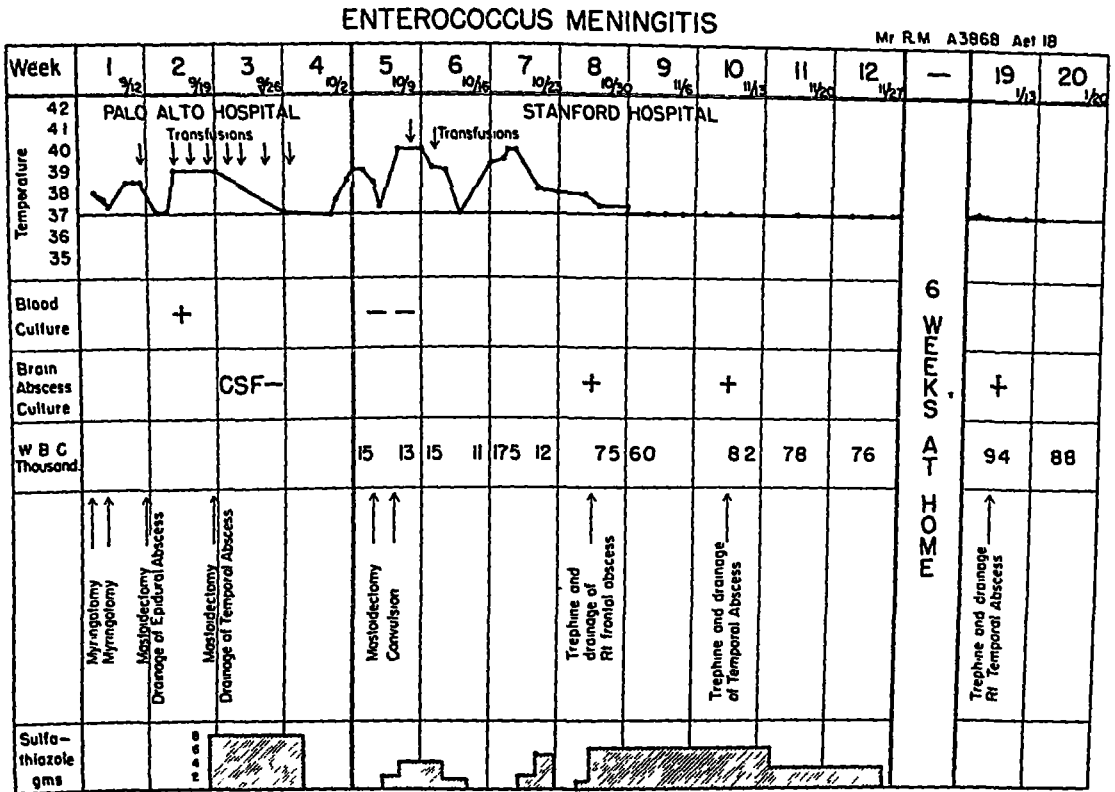


FIG 1

Laboratory studies showed the red count to be 4,670,000 and the hemoglobin 82 per cent (Sahli), the white blood count 15,000 per cubic millimeter with 75 per cent polymorphonuclears, 18 per cent lymphocytes and 7 per cent mononuclears. The urine was normal. The second day a very radical mastoidectomy was performed and part of the brain which herniated into the wound was removed with the electrocautery. Two days later he suffered a typical Jacksonian seizure which began in the left foot and became generalized. During the following week 4 grams per day of sulfathiazole were administered by mouth, and the powdered drug was blown in the mastoid wound. Gradual improvement followed and the temperature approached normal. Ventriculography was performed on November 1 because of continuing headache, and the signs of a mass in the right frontal lobe were demonstrated. A large abscess was discovered in this area through a trephine opening, and 75 cubic centimeters of thick pus were evacuated from which a streptococcus with alpha hemolysis was obtained in pure culture.

Six grams of sulfathiazole were administered daily by mouth for the following three weeks and then 3 grams per day for two weeks. The general physical condition improved steadily but on November 15 it was felt that another abscess might be present in the right temporal area, and a collection of pus from which a similar streptococcus was obtained in culture was evacuated through a trephine opening in this region. From this time on clinical improvement was striking, and the patient left the hospital on December 3, apparently well.

On January 13, 1941, he returned to the hospital having had a convulsion 24 hours earlier. Physical examination was within normal limits except for a tender area in the right temporal region, the temperature being 37.8°C , pulse 80, the leukocyte count 9,400 and the hemoglobin 86 per cent (Sahli). An opening was made through the skull over the right ear at the point of greatest tenderness, and a thick-walled abscess was discovered. This was drained and explored, and no connection was found with any of the previous abscesses. No sulfonamides were administered. His post-operative course was uneventful and he left the hospital on January 20. When last seen on January 29, 1941 he appeared to be absolutely well.

Bacteriology The organisms isolated from the blood and from meningeal abscesses on three occasions appeared to be identical. These streptococci grew in rough colonies on blood agar and formed large areas of bright green alpha hemolysis. They grew well at temperatures of 10°C and 45°C in the presence of 6.5 per cent sodium chloride and 10 per cent methylene blue. Gelatine was not liquefied. The antigen obtained from these organisms formed a precipitate in the presence of serum of the Lancefield Group D. These were the biological and serological criteria for the identification of the enterococci as described by Sherman¹⁴.

Comment The inclusion of this case under the general classification of meningitis is open to some question since there was never a diffuse or generalized involvement of the meninges. At operation, however, none of the localized abscesses penetrated the cerebral cortex. In every instance the infection lay immediately beneath the dura mater and may be properly classified as a localized, subacute meningitis.

An otitis media provided the portal of entry, and the presence of a positive blood culture early in the illness indicates a widespread dissemination of the organisms. Later there was localization in circumscribed areas of the meninges. At operation it was felt that these collections of pus were not all connected, but this is not susceptible of proof.

The organism isolated from the blood and meninges is not identical with the enterococci derived from the normal stool, but the biological and serological reactions were typical of this group of streptococci as described by Sherman.

Enterococci have been notably resistant to sulfonamide therapy¹⁷ and sulfathiazole has been shown¹⁸ to have very little more effect in urinary tract infections due to these organisms than the earlier drugs. The response to chemotherapy in this case was not dramatic, although it may have assisted in carrying the patient over the earlier acute phase. Drainage of the mastoid bone and local abscesses was necessary before cure was effected.

Case 3—Lancefield Group H Meningitis Mrs. C. J., a 65-year-old white female housewife, entered the hospital August 3, 1940, with a complaint of headache and

stiff neck of 48 hours' duration. The family history was unimportant as was the past history, except for the fact that she had suffered from sinusitis for many years and had undergone left simple antrotomy in 1925. The present illness began four days before entry with the development of an acute upper respiratory infection with headache which was diagnosed by her physician as acute frontal and maxillary sinusitis. Her clinical course was uneventful until the day before entry when her temperature rose to 100.2° F, and headache and dizziness developed. Within a short time stiff neck appeared, she became irrational and was brought to the hospital. Physical examination revealed a flushed, stuporous, elderly woman. The temperature was 40.2° C, the pulse 120 per minute, the respirations 24 per minute, the blood pressure 132 mm Hg systolic and 76 mm diastolic. No tenderness, edema or evidence of periostitis was demonstrated over the paranasal sinuses. The examination of the eyes revealed right lateral rectus weakness, but the pupils were equal in size, reacted to light and accommodation, and the fundi were normal. No abnormalities were seen in the mouth or nasopharynx. The neck was very stiff. The chest was clear to auscultation and percussion, the heart was of normal size, with regular rhythm, and no murmurs were heard. The abdomen was not remarkable. Moderate general motor weakness of the extremities was present, the Kernig sign was positive, the reflexes were sluggish but sensation was intact. The laboratory studies showed a hemoglobin of 88 per cent (Sahli), a red blood count of 5,200,000, a leukocyte count of 15,600 of which 66 per cent were polymorphonuclears, 29 per cent lymphocytes and 5 per cent monocytes. The Wassermann reaction was negative, the urine normal, and the blood culture sterile. Spinal puncture was performed immediately after admission, the pressure was found to be 120 millimeters of water and the dynamics were normal. Twenty-four hundred cells were present, of which 89 per cent were polymorphonuclear leukocytes and 11 per cent lymphocytes. The protein content was 21.2 milligrams. Cultures revealed an alpha hemolytic streptococcus. The patient's hospital course is shown in figure 2.

Twenty grams of sulfanilamide were administered by mouth in the first 72 hours. During this interval the temperature remained elevated and a lumbar puncture revealed spinal fluid essentially similar to that obtained two days before. The concentration of sulfanilamide was 117 milligrams per 100 cubic centimeters. Sulfapyridine therapy was instituted at this time and within 24 hours striking improvement had occurred. The cerebrospinal fluid showed a striking fall in total cell count, a rise in glucose content, and the cultures became sterile. Drug therapy was continued for nine days in gradually decreasing dosage. Her hospital course during this time was uneventful except for the development of a moderate secondary anemia which was combated by transfusion of whole blood. Cerebrospinal fluid obtained upon the eighth hospital day was practically normal. Two sharp rises in temperature in the third and fourth weeks were believed to be due to reactivation of her sinus infection. It was therefore, determined to undertake radical antrotomy, ethmoidectomy and sphenoidectomy. This operation was performed on the left in the fifth hospital week. When the sphenoid sinus was opened it was discovered that an imperfection existed in its roof so that only the mucous membrane separated the sinus from the dura mater. This area was regarded as the probable site of extension of the infection to the meninges. A large opening was provided from this region into the nose in the hope that subsequent difficulties might be avoided. Her postoperative convalescence was uneventful. She left the hospital near the end of the seventh week, and when last seen, four months later, was in good health.

Bacteriology. The organism isolated from the spinal fluid was an alpha hemolytic streptococcus which formed small smooth colonies on blood agar plates. It failed to grow at 10° C and 45° C in the presence of 65 per cent sodium chloride or 10 per cent methylene blue. When studied by a modification of the Lancefield technic precipitate was formed with Group H serum.

per minute, the respirations 30 per minute. The skin was warm and clear and no petechiae were seen. The pupils were equal in size and reacted to light and accommodation. The lateral rectus muscle of the right eye was paralyzed, the ocular fundi were normal. There was a large tender swelling in the region of the right parotid gland. The ears were not remarkable. The right Stenson's duct was observed to be inflamed and purulent material was expressed from it by pressure over the parotid mass. The nasopharynx was normal and the neck was not stiff. Examination of the chest revealed moist râles and dullness at the right base posteriorly. The heart was not enlarged, rhythm was regular and no murmurs could be heard. The blood pressure was 120 mm Hg systolic and 75 diastolic. The liver extended 8 centimeters below the right costal margin, the spleen was not felt. The genitalia were normal, as were the extremities. Kernig's sign was not elicited. Laboratory examination of the blood showed a red blood count of 4,820,000, hemoglobin of 98 per cent (Sahli), and leukocyte count of 18,550 of which 78 per cent were polymorphonuclears, 18 per cent lymphocytes, 4 per cent monocytes. The urine was normal, the Wassermann reaction negative. Roentgen-rays of the skull and chest showed no abnormalities. Culture of the blood revealed streptococci with alpha hemolysis. He remained in the hospital five days, the clinical course being illustrated in figure 3.

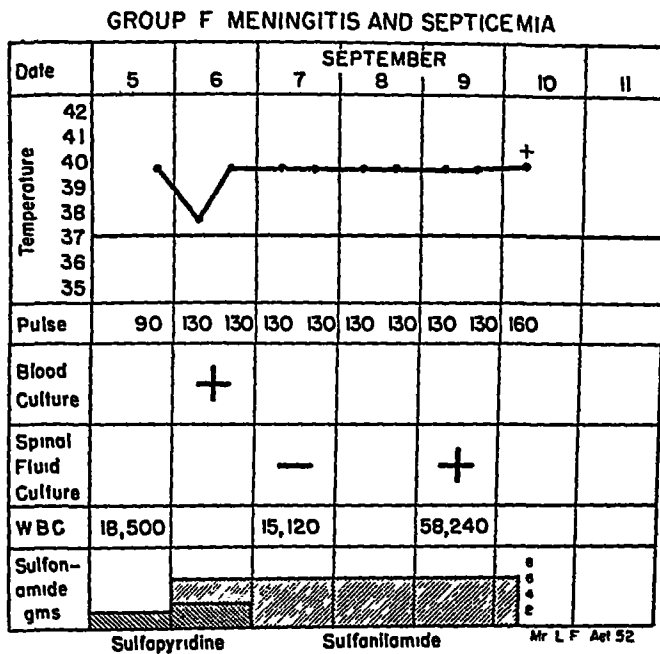


FIG 3

Five grams of sulfapyridine were administered by mouth in the first 24 hours followed thereafter by 1 gram of sulfanilamide every four hours for the duration of his disease. On the second hospital day he became comatose, the neck definitely stiff and Kernig's sign positive. Lumbar puncture at this time revealed a cloudy fluid containing 850 cells per cubic millimeter of which 96 per cent were polymorphonuclears. Culture of this specimen showed no growth but that of one obtained two days later showed a streptococcus with alpha hemolysis similar to that obtained from the blood culture.

In spite of intensive supportive therapy the patient became more deeply comatose, temperature and pulse remained elevated, the leukocyte count increased to 58,000 cells per cubic millimeter, and he died September 10, 1940

Bacteriology The organism obtained in the blood and spinal fluid was a streptococcus which formed green pigment on blood agar. It failed to grow at 10° C and 45° C in the presence of 6.5 per cent sodium chloride and 10 per cent methylene blue. Its antigen precipitated strongly in the presence of serum of the Lancefield Group F.

Comment This is a case of fatal sepsis and meningitis caused by an alpha hemolytic member of the Lancefield Group F. Members of this group have usually been regarded as frankly hemolytic but Hare¹⁹ has shown that, of a group of strains of streptococci from the nose and throat which failed to form soluble hemolysin, 25 per cent were in Group F and 50 per cent in Group H.

Extension of infection following extraction of a tooth with cellulitis of the face, parotitis, sepsis and meningitis was the course of events in this case. The means by which the infection was transmitted to the meninges is not clear.

Sulfanilamide was the therapeutic agent used. From the experience of case 3 it seems very possible that sulfapyridine or perhaps sulfathiazole would have offered a greater possibility of a satisfactory result. The presence of extensive cellulitis of the face and septicemia would have made the prognosis very grave under any circumstances.

DISCUSSION

These cases are presented for the purpose of emphasizing certain facts. The first is that the streptococci etiologically concerned in meningitis may be shown to be of many distant varieties when studied by suitable biological and serological methods. Evidence is presented from the literature which indicates that 80 per cent of the strains of streptococci isolated from cases of meningitis are hemolytic and practically all of these are members of the Lancefield Group A. Case 1 indicates that other types of hemolytic streptococci may occasionally invade the meninges. It is possible that certain cases in which these more unusual groups of organisms are involved have a milder clinical course, since the patient presented here was recovering before chemotherapy was instituted. It is, therefore, suggested that some of the previously reported instances of spontaneous recovery might have been caused by such organisms.

Secondly, it is apparent from the bacteriological studies on the three strains of non-hemolytic streptococci isolated from cases 2, 3 and 4 that widely different organisms were involved. It is important to bear in mind that such differences exist among the members of the non-hemolytic streptococci in order that suitable studies may be performed which will enable correct therapeutic and prognostic inferences to be accumulated and evaluated.

Chemotherapy appears to have been of very real value in case 3. A dramatic clinical improvement followed the change from sulfanilamide to sulfapyridine. In cases 1 and 2 the effect of the use of sulfonamides was much less clear but it is probable that they were of some help. Death occurred in case 4, but it is important to point out that sulfanilamide was used rather than sulfapyridine or sulfathiazole. This evidence suggests, and an analysis of the few previously described cases partially confirms the fact that sulfapyridine has a very definite therapeutic effect in cases of non-hemolytic or *Streptococcus viridans* meningitis. By inference with the results obtained in other infections sulfathiazole should be of equal value if a sufficient concentration can be maintained in the cerebrospinal fluid. This is usually accomplished without difficulty. The use of sulfanilamide in such cases appears to be contraindicated as it is probably therapeutically ineffective.

SUMMARY

1 Seventeen per cent of all cases of bacterial meningitis are caused by streptococci.

2 Eighty per cent of these organisms are hemolytic and predominantly members of the Lancefield Group A, 20 per cent are non-hemolytic or form green pigment on blood agar.

3 The mortality rate of meningitis due to both types of organisms is 95 per cent without effective therapy.

4 With the use of sulfonamides the mortality is only 20 per cent.

5 Four cases of meningitis due to unusual streptococci are presented. The etiological agent in one was a hemolytic streptococcus of the Lancefield Group B, in the second an enterococcus, in the third a non-hemolytic member of Group H, and in the fourth a non-hemolytic member of Group F.

6 Recovery occurred in three cases and death in one.

7 Sulfonamides exerted a doubtful effect on two cases and brought about dramatic improvement in a third treated with sulfapyridine. Sulfanilamide failed to influence the course of the fatal case.

8 Sulfapyridine is a definitely effective agent in non-hemolytic or "viridans" streptococcal meningitis. Sulfathiazole may also be of value.

9 Sulfanilamide is contraindicated in these infections.

ACKNOWLEDGMENT

The author wishes to thank Dr. Frederick Fender, Dr. Robert McNaught, Dr. LeRoy H. Briggs and Dr. John Brown for their courtesy and cooperation in permitting observations on three of these patients.

BIBLIOGRAPHY

- 1 LANCEFIELD, R. C. A serological differentiation of human and other groups of hemolytic streptococci, Jr. Exper. Med., 1933, 111, 571.
- 2 NEAL, JOSEPHINE. The treatment of acute infections of the central nervous system with sulfanilamides, Jr. Am. Med. Assoc., 1938, 61, 1353.

- 3 CADHAM, F T Streptococcus meningitis (with a report of eight cases two recoveries), Canad Med Assoc Jr, 1936, xxxv, 648
- 4 HARE, R Sources of haemolytic streptococcal infection of wounds in war and civil life, Lancet, 1940, 1, 109
- 5 THOMAS, A Purulent meningitis produced by minute hemolytic streptococcus, Jr Mt Sinai Hosp, 1939, v, 702
- 6 LANCEFIELD, R C, and HARE, R A serological differentiation of pathogenic and non-pathogenic strains of hemolytic streptococci from parturient women, Jr. Exper Med, 1935, lxi, 335
- 7 ZELIGS, M Streptococcic meningitis report of two cases with recovery, Am Jr Dis Child, 1935, 1, 497
- 8 ROSENBERG, L, and NOTTLEY, H W Recovery from streptococcus meningitis, ANN INT MED, 1931, iv, 1154
- 9 GRAY, H J Streptococcic meningitis Report of case with recovery, Jr Am Med Assoc, 1935, cv, 92
- 10 TRACHSLER, W H, FRAUENBERGER, G S, WAGNER, C, and GRAEME-MITCHELL, A J Streptococcic meningitis, Jr Pediat, 1937, xi, 248
- 11 TOOMEY, J A, and KIMBALL, R E, JR Meningitis caused by *Streptococcus hemolyticus* and treated with sulfanilamide, Jr Am Med Assoc, 1939, cxii, 2586
- 12 LOVE, J W Non-hemolytic streptococcic meningitis case successfully treated with sulfanilamide and prontosil, Jr Lab and Clin Med, 1938, xxiii, 482
- 13 MITCHELL, W J, BOWFR, A G, and HAMILTON, P M The use of sulfapyridine in *Streptococcus viridans* meningitis, Am Jr Med Sci, 1940, cc, 75
- 14 SHFRMAN, J M The streptococci, Bact Rev, 1937, 1, 1
- 15 FULLER, A J The formamide method for the extraction of polysaccharides from haemolytic streptococci, Brit Jr Exper Path, 1938, xix, 130
- 16 BROWN, J H A simplified method for grouping hemolytic streptococci by the precipitin reaction, Jr Am Med Assoc, 1938, cxi, 310
- 17 HELMHOLTZ, H F The bactericidal power of the urine after the administration of prontosil by mouth, Proc Staff Meet, Mayo Clin, 1937, xii, 244
- 18 RANTZ, L A Unpublished observations
- 19 HARE, R The classification of haemolytic streptococci from nose and throat of normal human beings by means of precipitin and biochemical tests, Jr Path and Bact, 1935, xli, 499

RECENT ADVANCES IN THE CARE OF THE COMATOSE PATIENT*

By BARNETT A. GREENE, M D, *Brooklyn, New York*

THE comatose patient, regardless of the cause of the coma, requires special therapeutic consideration. Coma does not merely indicate an advanced stage of the underlying disease but also complicates it because unconsciousness adds its own characteristic burdens to those of the primary disease. The coma which is of interest to us is that degree of unconsciousness in which the protective reflexes are decreased or absent. The severity of the physical changes which are the sequelae of coma is directly in proportion to the depth and duration of the coma. Because of the opportunities provided by his daily contacts with unconscious patients, the anesthesiologist is able to make many observations which are widely applicable to a general consideration of the state of coma. The patient who is long maintained in an unconscious condition by barbiturate poisoning or an eight-hour inhalation anesthesia for brain surgery—these comatose states offer the anesthesiologist an extensive proving-ground for the evaluation of measures designed to protect and care for the unconscious patient. It is because of these experiences and the emphasis on training in applied pharmacology and physiology of the most direct type seen anywhere in the clinical practice of medicine that the anesthesiologist has become, of late, a valuable member of the hospital team faced with the problem of the comatose patient.

The unconsciousness of the patient adds a tremendous burden to the therapeutic load carried by his physician for he must actively attend to almost every vital function, more specifically, respiration, body temperature, the intake of fluid, minerals and vitamins, excretion and peripheral circulation.

Let us consider each of these functional requirements in turn.

Urinary excretion is of great importance and demands detailed consideration of the fluid and mineral intake as well as meticulous attention to the method and frequency of bladder emptying. We have seen several instances of bladder paresis persist two weeks after a patient had recovered from the unconscious state only because the bladder was permitted to become over-distended and atonic. The maximum volume of a normal bladder is 400 cc.¹ If catheterization releases a volume much greater than this the patient is likely to develop a hypotonic bladder. When faced by this likelihood the prompt use of bladder contractors, such as prostigmin 1.2000 every three hours for five doses, and frequent emptying of the bladder will decrease the number of catheterizations and the tendency toward bladder infection. Delay in emptying the bladder is often due to the physician's desire to decrease the number of catheterizations to minimize urethral and bladder trauma.

* Received for publication June 16, 1941

The patient who is likely to remain unconscious for more than six hours should have a retention catheter and the bladder should be emptied every four to six hours, depending on the findings of bladder percussion. A bladder that is percussible or palpable should be promptly emptied. The use of neoprontosil or sulfanilamide in 40 grain doses per day is a valuable prophylactic against urinary infection in patients requiring repeated bladder catheterization or instrumentation.

The urinary output of the unconscious patient should not fall below 1000 c c per 24 hours. If this volume is maintained, we may be sure that there is sufficient water in the body to allow efficient temperature regulation and adequate nitrogenous excretion.²

Intimately related to the urinary output is the intake of sodium. The presence of an excessive quantity of sodium ions in the tissues inevitably leads to the retention of water to enable the tissue fluids to remain isotonic.³ This tendency toward keeping the normal status quo of the tissues and blood constant is so vital that it takes precedence over the requirements of the kidneys. Thus, an excessive sodium intake may lead to an inadequate urinary output even though the intake of water would otherwise be sufficient. It is very rare that an inadequate amount of salt is given in the absence of vomiting, diarrhea, hemorrhage, or profuse perspiration. On the other hand, an excessive salt intake is very common in the comatose patient because the daily salt requirement of the healthy adult is only 4-5 gm.⁴ and one liter of normal saline contains 9 gm. of sodium chloride. If the salt or saline were administered only by mouth, we might depend on the gastrointestinal mucosa to absorb the needed amount and reject the remainder. Excessive sodium chloride administration by mouth leads only to diarrhea. But the comatose patient receives his fluids by clysis or infusion and the tissues are, therefore, forced to accept the salt and make the best of it by retaining water to keep the tissue fluids and blood at normal osmotic pressure.⁴ If kidney function is normal and an abundant amount of "free" water (water not required to maintain normal osmotic pressure) is present, it is possible for the urinary output to rid the body of the excessive number of sodium ions. Very often, however, the renal function in coma, especially in the surgical patient, is also depressed.⁴ Thus salt and water retention persists, latent edema increases and, after about five liters of edema fluid have accumulated, there appears obvious evidence of edema, such as pitting on pressure, hydrothorax or pulmonary râles. Salt retention may be so extensive as to lead to a marked increase in blood volume, venous pressure and heart failure. This is very likely to occur when the comatose patient is given desoxycorticosterone acetate (cortate) or whole adrenal cortical extract for the prevention or treatment of shock.⁵ We do not decry the use of adrenal cortical extract, in fact, we urge its use.⁶ But we wish to spread this warning against the uncontrolled administration of salt and cortical hormones.

If parenteral fluid and saline are administered with the following points in mind there is little likelihood of harm.

(a) It is the quantity of sodium ion rather than the quantity of water that determines the occurrence of edema or cardiac overloading

(b) The administration of a liter of 5 per cent glucose in distilled water following each liter of normal saline provides plenty of "free" water

(c) The dehydrated patient has already lost a volume of tissue fluid equal to 6 per cent of his body weight⁷

(d) Every liter of body fluid lost requires replacement with a liter of normal saline

Edema fluid is most harmful when it accumulates in the viscera of the thorax and least harmful when present in the tissues of the sacral region or lower extremities. Edema fluid is influenced by gravity. The shift of tissue fluid to the pleura and lungs and great veins of the chest decreases the pulmonary vital capacity, increases dyspnea, and favors the appearance of pulmonary edema. It is, therefore, necessary to avoid placing every comatose patient routinely in the horizontal or Trendelenburg posture. In the presence of subcutaneous edema, the semi-sitting position may be advantageously employed if shock, vomiting and profuse bronchial secretions are absent. These symptoms, however, make the Trendelenburg position preferable in spite of its disadvantageous effect of shifting edema fluid to the chest.

It is apropos here to comment that the Trendelenburg position for the treatment of shock is not as beneficial as its universal use might imply. In the therapy of syncope associated with vasodilatation, the common fainting spell, it is of known and proved value⁸. In peripheral circulatory failure associated with spinal anesthesia, the Trendelenburg position has been shown by CoTui to be of very transient and little value. And yet, it is in this type of shock that most surgeons would agree that the Trendelenburg position is indicated. Thus, common usage is no criterion of usefulness. In the prevention or treatment of peripheral circulatory failure due to decreased blood volume, which is the usual and more serious type of shock, it is probably of little value because the maximum mobilization of tissue fluids and pooled blood has already been secured by the operation of more fundamental and effective protective mechanisms such as the contraction of arterioles, veins and venules and the increased osmotic pressure of the concentrated blood always associated with shock.

The characteristic and usually fatal complications of the comatose state (whether the coma is due to alcohol, morphine, ether, cerebral hemorrhage, or pneumonia), if the coma is deep and lasts more than a few hours, are pulmonary edema and pulmonary infection. The factors which favor their appearance are many, so many that in any individual case it is difficult to single out a specific cause. Usually the pulmonary edema and infection are the result of the interaction of several pathological processes. Chief among these causes are

1. Aspiration
2. Partial respiratory obstruction
3. Generalized tissue edema
4. Shock
5. Anoxia
6. Primary pulmonary infection

1 The aspiration of saliva and mucus is always to be feared in the unconscious patient, for the laryngeal and cough reflexes, those "watchdogs of the lungs," are usually absent or markedly depressed. Even more likely is aspiration to occur if the patient is vomiting or regurgitating. It is because of this danger that the stomach of the unconscious patient must be kept empty.⁹ Even when throat suction is constantly used through an open mouth under direct vision, as in a tonsillectomy under general anesthesia, aspiration occurs in a great majority of cases as was demonstrated by Myerson, who performed bronchoscopic examination routinely on a series of such cases.¹⁰ The presence of stagnant mucus in the tracheobronchial tree is a potent factor in the pathogenesis of pneumonia according to the laboratory studies of Lockwood,¹¹ and in the production of atelectasis as demonstrated both clinically and experimentally by Coryllos.¹²

2 Partial respiratory obstruction is so easy and common in the anesthetized patient that every anesthetist insists on the use of an artificial airway in the maintenance of deep anesthesia for longer than a few minutes. Coma unrelated to anesthesia is accompanied by the same relaxation of muscle and tissue tone so that there is a great tendency for the respiratory tract to be obstructed by the falling back of the tongue, by the indrawn pharyngeal walls and the partially adducted vocal cords. Should anoxia and tissue edema also be present, then there is added another obstructing factor, swollen pharyngeal and laryngeal walls.¹³

Partial respiratory obstruction leads to pulmonary edema through two mechanisms. (1) Anoxia increases the permeability of the capillaries,¹⁴ including those of the lungs, and the alveoli become filled with a transudate. (2) The "sucking" effect of the marked inspiratory efforts and the increased intrathoracic negative pressure which result from the partial respiratory obstruction. This latter mechanism of causing pulmonary edema has been only recently clearly demonstrated by Barach.¹⁵

Partial respiratory obstruction in coma must be treated in exactly the same way as in anesthesia, namely, by the insertion of a proper airway. If a pharyngeal airway is insufficient, then an endotracheal tube should be inserted under direct vision laryngoscopy as it is during endotracheal anesthesia. The endotracheal catheter is well tolerated for many hours and even days if its position is not disturbed frequently. The endotracheal tube not only guarantees an open respiratory tract but also prevents the inhalation of mouth secretions and vomitus and facilitates the non-traumatic removal of bronchial

secretions and pulmonary edema by suction through a catheter, easily and frequently inserted into the endotracheal tube ^{9, 16}

We wish to note here that the use of atropine in the prevention or treatment of pulmonary edema is illogical. Edema fluid is the result of exudation or transudation and is not the product of glandular secretion. Atropine blocks bronchial glandular secretion but does not affect the exudation or transudation of pulmonary edema. Atropine in the unconscious patient serves only to prevent sweating and thus may interfere with body temperature regulation.

3 Generalized tissue edema of any origin inevitably tends toward pulmonary edema because of the recumbent position of the unconscious patient, the large blood content of the lungs and the vast capillary surface area in the lungs. Of all the organs which edema usually affects, the lungs are the most vital. Recovery from coma is sometimes prevented only by the anoxia caused by pulmonary edema. Oxygen therapy in the presence of gross pulmonary edema is always unsatisfactory unless it is preceded by mechanical clearing of the pulmonary passages.

4 Shock often leads to pulmonary edema and bronchopneumonia because shock is characterized by a diffuse and marked increase of capillary permeability including the capillaries of the lungs. This relationship has been beautifully demonstrated experimentally by the classical work of Virgil Moon ¹⁷. The prevention or treatment of pulmonary edema necessarily involves the prevention or treatment of shock or peripheral circulatory failure. We shall discuss later and at length the subject of peripheral circulatory failure in the comatose patient.

5 Anoxia can be a primary cause of pulmonary edema by its action of increasing capillary permeability. More often, however, anoxia is a secondary and complicating sequel of pulmonary edema, thus tending to perpetuate the pulmonary edema. The anoxia of the comatose patient, to be properly treated, should be differentiated as to its type, i.e., whether the anoxia is of the anemic, histotoxic, stagnant or anoxic group as defined by Barcroft ¹⁸.

6 Pulmonary infection and pulmonary edema are often found together, clinically. Either one may lead to the other. Pulmonary infection promotes pulmonary edema by causing a massive outpouring of inflammatory exudate through the lung capillaries. Pulmonary edema favors infection by providing an excellent culture medium for the bacteria of the tracheo-bronchial passages and by obstructing the natural clearing mechanisms of the lungs. Just as the obstructed bladder is sure to become the seat of infection so is the obstructed lung certain to develop a pneumonitis. We must adopt the therapeutic attitude of the urologist and always look for and treat any obstructing factors in the lungs, whether it is a mucous plug or edema fluid, when we attempt to prevent or treat a pneumonia.

Morphine has no place in the treatment of pulmonary edema even though

convention has sanctioned it. Morphine anesthetizes the cough reflex, the chief mechanism of the lungs in their effort to maintain an unobstructed airway. This expulsive mechanism is even more important in the stuporous or unconscious patient with pulmonary infection or pulmonary edema.

Stimulants are almost always found listed in the order sheets of every coma case that dies. In fact, they are so frequently used as a last-hour desperate measure that the term "medical last rites" has been applied to this usually hopeless and often harmful series of injections of coramine, epinephrine, strychnine, caffeine, digitalis, etc. Many physicians have considered such drugs as coramine and strychnine to be valueless under all circumstances because they have always used these drugs on terminal cases or on improper indications. The manufacturers of such drugs as coramine or metrazol are partly to blame for this therapeutic nihilism because they have been guilty in the past of encouraging the indiscriminate use of their products. The chief reason, however, for the incorrect use of stimulants in comatose patients is a lack of correct pharmacological understanding of the relationship of the large variety of stimulants to coma.

(a) The analeptic stimulants, namely, coramine, metrazol and picrotoxin, are chiefly of value in combating coma due to the depressant drugs, e g, morphine, barbiturates, paraldehyde, chloral hydrate, etc ^{19, 20}. In these drug-produced comas we can obtain brilliant results, as, for example, in the following case.

A 28-year-old eclamptic was delivered by caesarean section but continued on to have two more convulsions in the next six hours. In the first 12 hours after operation she received two doses of morphine sulphate grain $\frac{1}{4}$, 2 c c of 50 per cent magnesium sulphate by hypodermic and 30 grains of chloral hydrate by rectum. She was mildly cyanotic despite oxygen therapy, breathed rapidly and shallowly, the lungs were filled with loud bubbling râles, blood pressure was 80 mm of Hg systolic and 40 diastolic, and she was deeply comatose. Her depressed central nervous system and peripheral circulatory system were regarded by her attending physician as terminal events. But the anesthesiologist considered her coma to be only in part due to exhaustion following convulsive activity and that the depressant drugs administered for control of eclampsia were also responsible for her depressed state. The intravenous injection of 3 c c of coramine produced an immediate and marked stimulation of restlessness and pharyngeal reflexes. After a few minutes her condition returned to its previous status but the repetition of intravenous coramine, 3 c c, secured immediate awakening, mumbling speech and marked restlessness, and the blood pressure rose to 110 systolic and 60 diastolic. She was out of danger within 12 hours. Of course, other therapeutic measures advised in this paper were also used, such as aspiration of the trachea, the insertion of an airway, and the inhalation of 100 per cent oxygen.

(b) The sympathico-mimetic stimulants, such as epinephrine and ephedrine, are indicated in the comatose state associated with Stokes-Adams seizures, allergic attacks or extensive vasodilatation as in ordinary syncope, spinal anesthesia or excessive drug depression ²⁰. These drugs are not only effective peripheral vasoconstrictors but also possess some of the cerebral-

awakening and respiratory-stimulating qualities of the above mentioned analeptics²¹ In fact, the analeptic and sympathico-mimetic drugs are more effective when employed synergistically in coma caused by excessive doses of hypnotics or narcotics²⁰

(c) The purine group of stimulants, namely, caffeine and theophylline, are of little value in coma except for the parenteral use of caffeine in lowering intracranial pressure and the intravenous injection of aminophylline for the correction of asthmatic²² and Cheyne-Stokes types of breathing

(d) Strychnine is an unusual stimulant in that its predominant effect is on the spinal cord in which it increases irritability by lowering the synapse threshold Its chief value lies in a marked ability to increase the tone of the voluntary musculature, as demonstrated by Yandell Henderson²³ This drug is most useful for the prolonged maintenance of good muscular tone in the comatose patient threatened with peripheral circulatory collapse due to a decreased supportive action of relaxed musculature on the intramuscular capillary and venous blood vessels

The dose and method of administration of stimulants are very important in obtaining the best results in coma The intravenous route is preferred because the desired results are obtained immediately and dosage can be more promptly and accurately judged Coramine 5 c c, metrazol 3 c c, or picrotoxin 1 c c, are the initial intravenous doses, they should be repeated every 15 minutes until the desired increase in reflex and cerebral activity is seen Facial twitching is the first sign of maximum effect and it must be allowed to disappear before continuing with the stimulant

Epinephrine is usually given in overdosage Two or three minims intravenously or 4-5 minims hypodermically is sufficient in the great majority of instances The toxic effects of epinephrine on the heart have not been sufficiently appreciated²⁴ Ephedrine sulphate $\frac{1}{2}$ c c (25 mg) intravenously is safer and longer-lasting than epinephrine²⁵ Neosynephrine $\frac{1}{4}$ c c intravenously or $\frac{1}{2}$ c c hypodermically is an excellent long-acting sympathetic stimulant which has the least disturbing effect on the cardiac rhythm or the cerebral cortex²⁶ It is the sympathetic-stimulating drug of choice in the presence of cardiac disease The excessive use of vasoconstricting agents is capable of causing shock by producing so intense an ischemia as to cause capillary damage²⁷ They are indicated in peripheral circulatory depression caused by depressant drugs or primary vasodilatation, they are contraindicated in hemorrhage or "secondary" shock

Strychnine sulphate is rarely used in sufficient amounts to secure a therapeutic effect The minimum dose is $\frac{1}{10}$ grain repeated every four hours

The comatose patient usually dies in peripheral circulatory failure with pulmonary edema and infection as terminal manifestations The comatose state favors the appearance of peripheral circulatory failure because there is

a widespread lowering of the muscular and tissue tone accompanying the severe central nervous system depression. All measures which increase muscular tone, such as strychnine, carbon dioxide inhalation, muscular activity and bandaging of the extremities, prevent the pooling of blood and tissue fluid in the tremendous capillary network of the muscles. The increased practice of measuring hemoconcentration should enable the clinician to begin shock therapy before the arrival of the relatively late sign of low blood pressure. The prophylaxis of decompensated shock is far easier and more effective than the treatment of obvious peripheral circulatory collapse. In the treatment of this condition we should depend more on intravenous saline, blood plasma and adrenal cortical extract than on epinephrine and other attempts to cause vasoconstriction in a patient whose vasoconstricting mechanism is operating at its maximum.

The central nervous system that is depressed is in need of increased oxygen irrespective of the cause of the coma. Space does not permit us to recite the results of the detailed studies of brain metabolism in the various types of coma, but it suffices to state that we may always expect that there is deficient oxygen delivery by the blood or uptake by the brain cells in coma. In the face of this derangement of oxygen metabolism the least that the clinician can do is to supply a maximum amount of oxygen. The inhalation of 100 per cent concentration of oxygen supplies the maximum amount of oxygen. This is not harmful when continued for not more than 12 consecutive hours, and it may be repeated for periods of 12 hours each when the administration is alternated with four hour periods of 50 per cent oxygen.²⁸ It seems to us that this dosage of oxygen is indicated in every case, for even a normal individual breathing 100 per cent O_2 absorbs an increased amount of oxygen into solution so that the total oxygen content of arterial blood is increased by 10–15 per cent (2.5 cc).²⁸ The use of a B-L-B or similar type of face mask enables one to give high concentrations of oxygen in a very effective and economical way.²⁹

SUMMARY

With the increased tendency of physicians to secure special training in anesthesiology and to study the physiology and pharmacology of the unconscious patient, we have witnessed many recent advances in the clinical care of all comatose patients. We have learned to detect early in the comatose patient the many abnormalities of the respiration, circulation, excretion, and salt and water metabolism. A valuable set of clinical measures, solidly grounded on scientific studies, is now available. The comatose patient has a more hopeful prognosis than ever before. If the physician approaches the comatose patient in a spirit of energetic optimism which encourages him to apply vigorously the measures recommended in this paper, many surprising and happy recoveries may be obtained in situations usually considered hopeless.

BIBLIOGRAPHY

- 1 NESBIT, R M, and GORDON, W G The neurogenic bladder, *Penna Med Jr*, 1940, xliii, 1261
- 2 LATIMER, E O Water balance, *Am Jr Surg*, 1939, xlii, 224
- 3 *Ibid* p 225
- 4 MADDOCK, W G, and COLLIER, F A Sodium chloride metabolism of surgical patients, *Trans Am Surg Assoc*, 1940, lviii, 38
- 5 WILLSON, D M, RYNEARSON, E H, and DRY, T J Cardiac failure following treatment of Addison's disease with desoxycorticosterone acetate, *Proc Staff Meet Mayo Clin*, 1941, xvi, 168
- 6 WEIL, P G, ROSE, B, and BROWNE, J S L The reduction of mortality from experimental traumatic shock with adrenal cortical substances, *Canad Med Assoc Jr*, 1940, xliii, 8
- SCUDDER, J Shock, 1940, J B Lippincott Co, Montreal
- 7 MADDOCK, W G, and COLLIER, F A Water balance in surgery, *Jr Am Med Assoc*, 1937, cviii, 1
- 8 CoTUI, F W Present scientific status of spinal anesthesia, Parts I and II, *Curr Res Anesth and Analg*, 1938, xvii, 146, 181
- 9 WATERS, R M Aspiration pneumonitis, an obstetric hazard, *Jr Am Med Assoc*, 1940, cxiv, 1391
- 10 LOWENTHAL, G Tracheobronchial aspiration of buccopharyngeal secretion during ether anesthesia, *Arch Otolaryng*, 1935, ii, 561
- 11 PICKRELL, K L Effect of alcoholic intoxication and ether anesthesia on resistance to pneumococcal infection, *Bull Johns Hopkins Hosp*, 1938, lxiii, 236
- 12 CORYLLOS, P N Post-operative pulmonary complications and bronchial obstruction, *Surg, Gynec and Obst*, 1930, l, 795
- 13 ROSS, S S, and FAIRLIE, H P Handbook of anesthetics, 5th ed, 1940, Williams and Wilkins Co, Baltimore, p 30
- 14 LANDIS, E M Micro-injection studies of capillary permeability effect of lack of oxygen on permeability of capillary wall to fluid and to plasma proteins, *Am Jr Physiol*, 1928, lxxxiii, 528
- 15 BARACH, A L The effects of inhalation of helium mixed with oxygen on the mechanics of respiration, *Jr Clin Invest*, 1936, xv, 47
- 16 HAIGHT, C Intratracheal suction in the management of postoperative pulmonary complications, *Ann Surg*, 1938, cvii, 218
- 17 MOON, V H, and KENNEDY, P J Pathology of shock, *Arch Path*, 1932, xiv, 360
- 18 BARCROFT, J Anoxemia, *Lancet*, 1920, ii, 485
- 19 ROVENSTINE, E A Use of picrotoxin in treatment of barbiturate poisoning, *Am Jr Med Sci*, 1938, cxcvi, 46
- MALONEY, A H, and TATUM, A L Cardiazol (Metrazol) and coramine cardio-respiratory stimulants, *Arch internat. de pharmaco dynam et de therap*, 1932, xlii, 200
- BURSTEIN, C L, and ROVENSTINE, E A Clinical experience with the newer analeptics, *Curr Res Anesth and Analg*, 1937, xvi, 151
- 20 BARLOW, C W Relative efficiency of a series of analeptics as antidotes to sublethal and lethal dosages of pentobarbital, chloral hydrate and tribromethanol, *Jr Pharmacol and Exper Therap*, 1935, iv, 1
- 21 SCHULTE, J W, TAINTER, M L, and DILLE, J M Analeptic activity of sympathetico-amines, *Jr Pharmacol and Exper Therap*, 1939, lxvii, 56
- 22 CARR, H A Treatment of acute attacks of bronchial asthma by intravenous injection of aminophylline, *Jr Lab and Clin Med*, 1940, xxv, 1295
- 23 HENDERSON, Y Adventures in respiration, 1938, Williams and Wilkins Co, Baltimore

- 24 SOLLMANN, T A manual of pharmacology, 5th ed, 1936, W B Saunders Co, Philadelphia, p 416
- 25 Ibid p 428
- 26 ORTH, O S, LEIGH, M D, MELLISH, C H, and STUTZMAN, J W Action of sympathomimetic amines in cyclopropane, ether and chloroform anesthesia, Jr Pharmacol and Exper Therap, 1939, lxvii, 1
- HENDERSON, V E The substances causing vasoconstriction, Anesthesiology, 1940, 1, 334
- 27 FREEMAN, N Decrease in blood volume after prolonged hyperactivity of sympathetic nervous system, Am Jr Physiol, 1933, ciii, 185
- 28 BOOTHBY, W M, MAYO, C W, and LOVFLACE, W R, JR. One hundred per cent oxygen indications for its use and methods of its administration, Jr Am Med Assoc, 1939, cxiii, 477
- 29 LOVFLACE, W R, JR Oxygen for therapy and aviation, Proc Staff Meet Mayo Clin, 1938, xiii, 646

THE CONCENTRATION OF CREATINE IN HEART, DIAPHRAGM, AND SKELETAL MUSCLE IN UREMIA *

By HARRY GROSS, M D , and MARTA SANDBERG, P H D ,
New York City

THE rôle of creatine in muscle metabolism has been well established. All voluntary muscles of vertebrates are rich in creatine, whereas smooth muscle contains relatively little. Muscle efficiency stands in a definite relationship to the amount of creatine present.

Numerous investigators have determined the creatine content of heart and skeletal muscle. As early as 1913 Myers and Fine¹ reported on muscle

TABLE I
Creatine Values of Human Muscles in Health and in Disease Obtained by Various Investigators

Investigators	Muscle Studied	Creatine Values in mg per cent
Denis	Psoas	360-421
Bodansky	Diaphragm, normal	309-331
Bodansky	Heart, normal	220
Bodansky	Psoas, normal	485
Seecof, Linegar and Myers	Left ventricle, normal	Range 150-300, average, 211
	Right ventricle, normal	Range 100-200, average, 148
	Pectoralis major, normal	Range 258-564, average, 394
Cowan	Heart, normal	202 ± 37
	Heart in pyelonephritis, uremia, bronchopneumonia and sepsis	117
	Heart in malignancy	117-134
	Heart in cardiac decompensation	144
	Heart in hypertrophy without decompensation	165 ± 30
	Heart in chronic nephritis	144-172
Herrmann, Decherd and Oliver	Left ventricle normal	175 ± 21
	Heart disease without failure	173
	Heart in hypertension without failure	198 ± 16
	Heart in coronary sclerosis	157
	Left ventricle in glomerulonephritis and uremia	159
	Left ventricle in anemia	157
	Heart in prolonged infections	119
	Left ventricle in congestive failure	122

* Received for publication October 7, 1940

From the Medical Division and Division of Laboratories, Montefiore Hospital for Chronic Diseases, New York City

TABLE I—*Continued*

Investigators	Muscle Studied	Creatine Values in mg per cent
Bodansky and Pilcher	Normal left ventricle	Range 38–295, average 159
	Normal right ventricle	Range 38–230, average 114
	Left ventricle in congestive failure	Range 38–265, average 139
	Right ventricle in congestive failure	Range 38–230, average 103
	Cardiac hypertrophy, left ventricle	Range 81–237, average 146
	Cardiac hypertrophy, right ventricle	Range 49–169, average 109
	Minimal heart disease, left ventricle	Range 97–273, average 175
	Minimal heart disease, right ventricle	Range 84–212, average 128
Linegar, Frost and Myers	Left ventricle, normal	200
	Right ventricle, normal	150
	Pectoralis major, normal	400
	Left ventricle, cardiac decompensation	175
	Right ventricle, cardiac decompensation	132
	Pectoralis major, cardiac decompensation	390
	Diabetes, left ventricle	195
	Diabetes, right ventricle	143
	Diabetes, pectoralis major	313
	Left ventricle in carcinoma	180
	Right ventricle in carcinoma	129
	Pectoralis major in carcinoma	340
	Left ventricle in uremia	287
	Right ventricle in uremia	210
	Pectoralis major in uremia	501
	Left ventricle in uremia with heart failure	176
	Right ventricle in uremia with heart failure	136
	Pectoralis major in uremia with heart failure	401
Constabel	Heart, normal	170–180
	Heart, fatty	60–120 rt and lt ventricle
	Heart, malignancies	70–100
	Heart, tetanus	80
	Heart, osteomyelitis	170–180
	Heart, kidney abscess	160
	Heart, puerperal sepsis	188
Myers and Fine	Abdominal muscle in peritonitis	396
	Leg muscle in sarcoma of leg	391

creatinine under normal conditions. They established the fact that urinary creatinine and muscle creatine are interdependent in a given species. Denis,² in 1916, studied the creatine content of normal psoas muscle.

Constabel,³ in 1921, was the first to determine the creatine content of human heart muscle. He found this to be 170–180 mg per cent for the

left ventricle, whereas it amounted to only 130 mg per cent for the right ventricle. Age and sex appeared to play no rôle. According to Seecof, Linegar and Myers⁴ both ventricles show the same creatine concentration at birth, but a difference in creatine content is established during the first year. Creatine concentration was increased in hearts hypertrophied to a certain degree, but beyond that level it showed a decrease. Linegar, Frost and Myers⁵ found the creatine values for the left ventricle higher than those for the right one in a number of species including the human. There was no apparent correlation of creatine content and heart weight but the average was slightly higher for heavier hearts. Creatine content was reduced in muscular exercise, chronic disease and congestive failure, reduced after an initial increase, in fasting, and variable in acute diseases.

Cowan⁶ studied the creatine values of 80 hearts, 48 of which were normal, 17 of which were from cases of decompensated heart disease, and 15 from patients with various diseases. Cardiac creatine was reduced in diseases accompanied by muscle weakness, cachexial disease and malignancies, but cases of sepsis showed normal values. He found the creatine content of hypertrophied hearts without failure to be between that of normal and that of decompensated hearts. He was of the opinion, however, that hypertrophied hearts have higher creatine concentrations than non-hypertrophied hearts.

Herrmann, Dechard and Oliver⁷ found that in four patients dying after acute coronary thrombosis the infarcted areas showed a striking loss of creatine as compared to the uninfarcted areas, the ratio being about two to one. In the uninfarcted area creatine was reduced to the amount found in congestive heart failure. The average creatine content of the left ventricle in cases of congestive heart failure was 30 per cent less than normal. Bodansky and Pilcher⁸ found the most marked variation in creatine content in patients with congestive failure and the least variation in those with minimal heart disease. Conditions burdening one side of the heart (like tuberculosis and pneumonia which predominantly affect the right side of the heart) caused the greatest decrease in creatine in that portion. Linegar, Frost and Myers⁵ found that the creatine content of neither voluntary nor cardiac muscle bore any direct relation to creatinine retention in the blood. However, in most cases with low creatine concentration for heart muscle there was heart failure.

Chanutin and Silvette⁹ state that in nephritis there is a marked accumulation of creatine as well as creatinine in the blood. Seecof, Linegar and Myers⁴ believe that retention of creatinine in renal disease causes a shift of the normal equilibrium between creatine and creatinine toward the creatine side. In this manner they explain the greatly increased concentration of creatine in cardiac and voluntary muscle in their cases of renal disease. The greatest concentration of creatine they found was in the left ventricle and voluntary muscle in two instances of renal arteriosclerosis with cardiac hypertrophy. Linegar, Frost and Myers⁵ also reported high creatine values

for cardiac and voluntary muscle in uremia without heart failure, reaching 500 mg per cent in voluntary muscle. In uremia with heart failure, creatine content of both the right and left ventricles and the pectoralis major was not as marked as in uremia without heart failure. There was no relationship of creatine concentration of muscle to creatinine concentration and CO_2 combining power of the blood. Herrmann and his co-workers,⁷ studying similar material, found low creatine concentrations of muscles. To our knowledge the only determinations of the creatine content of the normal human diaphragm are those of Bodansky,¹⁰ who reported three specimens which showed values ranging from 309 to 331 mg per cent. Since only these few figures were available, we estimated the creatine content of the diaphragm in normal human beings. Thus we were able to gauge the effect of uremia on the storage of creatine in the diaphragm. The normal diaphragms of 12 males and three females were obtained with one exception within 24 hours of death. In the majority of cases death was the result of accident or assault so that the tissues were as nearly normal as possible. Except for one specimen from a male child eight years of age, all were from adults.

TABLE II
Glomerulonephritic Group

Sex	Age	Primary Disease	Maximum Blood Chemistry Findings in mg per cent
F	20	Chronic glomerulonephritis, hypertension, uremic pericarditis with effusion	Urea N 104 Creatinine 8.3 CO_2 35 vol %
M	25	Chronic glomerulonephritis, congestive heart failure with ascites and bilateral hydrothorax	Urea N 211 Creatinine 10
M	44	Hypertension, diabetes mellitus, chronic glomerulonephritis, congestive heart failure	Urea N 108
F	56	Chronic glomerulonephritis, hypertension, diabetes, congestive heart failure	Urea N 75.6
M	69	Chronic glomerulonephritis, hypertension, myocardial infarction, congestive heart failure	Urea N 157.2 CO_2 32 vols % Creatinine 2.7
M	20	Chronic glomerulonephritis, hypertension	Urea N 115 Creatinine 6.5 CO_2 41 vols %
M	18	Chronic glomerulonephritis, terminal congestive failure	Urea N 202 Creatinine 15 CO_2 24 vols %
F	60	Chronic glomerulonephritis, diabetes, congestive failure $2\frac{1}{2}$ years	Urea N 81.6 Creatinine 4.6 CO_2 36 vols %

TABLE II (Continued)
Glomerulonephritic Group

Creatine, mg per cent			Heart Weight at Necropsy in Grams	Cause of Death
Heart	Muscle	Diaphragm		
116	312	183	300	Uremia
106	282	237	525	Uremia
68	—	70	410	Uremia
111	76	70	320	Sepsis Uremia
82	185	—	525	Uremia
113	395	246	500	Diffuse broncho- pneumonia
101	—	—	1770	Uremia
212	—	—	385	Infection and uremia

TABLE II (Continued)
Renal Arteriosclerosis

Sex	Age	Primary Disease	Maximum Blood Chemistry Findings in mg per cent
F	48	Rheumatic mitral stenosis and insufficiency, hypertension, renal insufficiency, congestive heart failure	Urea N 86.5 Creatinine 2.1
F	69	Hypertension, hemiplegia, renal insufficiency	Urea N 47.2
F	81	Ulcers of leg, renal insufficiency one month	Urea N 101 Creatinine 4.4
M	62	Rheumatic mitral and aortic disease, angina pectoris, congestive heart failure 7 years, syphilis	Urea N 82 Creatinine 2.1
F	58	Hypertension, diabetes 10 years, congestive heart failure 5 years	Urea N 87.5 CO ₂ 30 vols %
M	62	Hypertension 5 years, hemiplegia one year before admission	Urea N 155 Creatinine 2.1
M	52	Rheumatic mitral and aortic disease, anginal and progressive congestive failure 5 years	Urea N 209 Creatinine 6 CO ₂ 10 vols %
F	49	Hypertension, cardiac enlargement, congestive failure, malignant renal hypertension	Urea N 50 Creatinine 3.7

TABLE II (Continued)
Renal Arteriosclerosis

Creatine, mg per cent			Heart Weight at Necropsy in Grams	Cause of Death
Heart	Muscle	Diaphragm		
65	96	107	650	Uremia
198	—	190	340	Sepsis
106	—	97	350	Uremia
67	—	42	920	Progressive congestive ht failure
113	—	97	640	Cerebral insult
139	—	148	500	Uremia, recent myocardial damage
93	370	210	650	Uremia
151	300	183	—	Uremia

TABLE II (Continued)
Renal Obstruction

Sex	Age	Primary Disease	Maximum Blood Chemistry Findings in mg per cent
F	65	Carcinoma of stomach with generalized abdominal metastases	Urea N 83 3 Creatinine 4 5
M	52	Carcinoma of stomach with metastasis	Urea N 146 Creatinine 2 7
M	54	Carcinoma of bladder with extension to pelvis, bilateral hydroureter and hydronephrosis	Urea N 147
F	41	Carcinoma of breast with metastasis, metastasis to lungs, liver, spine	Urea N 100 Creatinine 5.3
M	62	Multiple myeloma with metastasis to ribs, right kidney, lymph nodes Chronic nephritis, hypertension	Urea N 129 Creatinine 5 3
F	55	Renal tuberculosis, post right nephrectomy, left kidney and ureter tuberculosis	Urea N 167 Creatinine 7 5
M	69	Chronic pulmonary, ileal, renal, ureteral and bladder tuberculosis, bilateral renal calculi	Urea N 75 5 Creatinine 2 2
M	35	Tuberculosis, pyelonephritis, ureteritis and cystitis, tuberculosis of the liver, lungs, spleen and prostate	Urea N 160 Creatinine 7 5 CO ₂ 15 vols %
F	40	Nephrolithiasis, pyelonephritis, contracted kidney, ureteritis cystica	Urea N 129 Uric acid 9 5 Creatinine 8 7
F	51	Bilateral congenital polycystic kidneys, cysts of liver and suprarenals	Urea N 260 Creatinine 4 6

TABLE II (Continued)

Renal Obstruction

Creatine mg per cent			Heart Weight at Necropsy in Grams	Cause of Death
Heart	Muscle	Diaphragm		
157	155	240	250	Uremia
156	223	192	300	Uremia
185	—	102	210	Bronchopneumonia
98	308	195	330	Left ventricular failure
129	362	388	300	Uremia
142	297	210	340	Sepsis
113	276	210	280	Uremia
87	—	187	265	Uremia
115	—	—	550	Uremia
138	—	125	240	Uremia

It appeared desirable also to study the creatine content of large and small hearts from uremic patients with and without heart failure. For purposes of comparison we also determined the creatine content of muscles of cases in which the heart was not diseased, as in renal tuberculosis and malignancies with uremia as the result of obstructive phenomena.

Findings Creatine was determined according to Rose, Helmer and Chanutin¹¹. Muscle samples were, in the majority of instances, obtained within 24 hours after death. The material consisted of specimens of heart, diaphragm and skeletal muscle obtained from eight cases of uremia secondary to chronic glomerulonephritis, eight cases of uremia secondary to renal arteriosclerosis, and 10 cases with obstructive and destructive renal lesions resulting in uremia. Diabetes occurred six times, four times associated with glomerulonephritis and twice with renal arteriosclerosis. In the obstructive group there were four malignancies, one multiple myeloma, three cases of tuberculosis including renal tuberculosis, one with calculus pyelonephritis and one with bilateral polycystic disease of the kidneys. The features common to all were the existence of chronic diseases and their termination in uremia.

Though grouping is difficult because of the marked overlapping of diseases one may divide the material into the three groups mentioned above. A further classification may then be made on the basis of heart size, congestive failure, cachectic diseases and infection. The difficulty of grouping the cases is increased by lack of knowledge of the causes of variations in

creatinine content of the muscles, and of the factors involved in any given instance

Most of the factors known to produce low creatinine values for muscle were present in one or another of our cases. Muscle weakness, chronic disease, chronic infection, malignancy, marked cardiac enlargement, congestive heart failure, cachexia and infection played a part. Severe acute sepsis, another cause of a low creatinine value in muscle, was terminal in some instances.

In the group with chronic congestive heart failure the etiological basis was rheumatic heart disease in two cases, essential hypertension in four, and chronic glomerulonephritis in five. All had cardiac enlargement, the usual finding in chronic congestive heart failure, irrespective of the etiological agent. Heart weights ranged from 320 to 1770 grams. The average creatinine content of the myocardium was 106 mg per cent. Although the creatinine in the skeletal muscle amounted to 370 mg per cent in one case, it was low in all the others, with an average of 218 mg per cent. The highest figure for diaphragm creatinine was 237 mg per cent in one instance, but the average for this muscle was 127 mg per cent. A relatively high figure for creatinine in one muscle did not mean a correspondingly high creatinine content in another.

The relationship of relatively small hearts weighing 300 grams or less to the creatinine content of muscle is an interesting one. Although creatinine figures are generally low, they are considerably higher than in chronic congestive heart failure. Average creatinine values were 135, 266 and 203 mg per cent for myocardial, skeletal and diaphragm muscle respectively. Again, no relationship existed between the creatinine figures for one muscle and those for another. The low creatinine values may be explained by consideration of the fact that carcinoma occurred four times, advanced renal tuberculosis three times, multiple myeloma, chronic glomerulonephritis and congestive heart failure once each in this group. In addition, Vincent's angina, sepsis and bronchopneumonia were also contributory factors to a low creatinine content in several of the cases.

In the group associated with cachexia, consisting of four cases with carcinoma, one with multiple myeloma, and three with tuberculosis, low creatinine figures were obtained. The creatinine values corresponded to those obtained in small hearts. Since hearts of this size were present in our cases, this may have been a contributory factor. The average for the heart was 133, for skeletal muscle, 270, for diaphragm, 215 mg per cent. Despite the small hearts and the absence of chronic congestive heart failure, chronic cachexia resulted in low creatinine findings in all the muscles studied, even though all these patients showed creatinine retention and uremia.

Five cases, including two with infections severe enough to produce gangrene, died of sepsis. The average creatinine content was 170 mg per cent for the myocardium, 187 for voluntary muscle, and 143 for diaphragm. In

two cardiacs creatine was within normal limits. One of these had been in chronic congestive heart failure and another had had hypertension. Evidently, in exceptional cases, congestive failure may not produce significant or actual decreases of creatine in the myocardium. Possibly creatinine retention in these two instances resulted in normal creatine values.

Four cases with moderate cardiac enlargement with heart weights ranging from 385 to 550 grams had had no congestive heart failure. The average creatine values were 145 mg per cent for the myocardium, 395 for skeletal muscle, and 197 for the diaphragm. The creatine content in all the muscles studied was slightly but definitely higher than in the group in failure. A contributory factor to low creatine values in this sub-group was the presence of infection in two patients and recent myocardial damage in another.

Since low creatine figures have been reported in the muscles in diabetes, those of six diabetics were analyzed. One had had hypertension, another, rheumatic heart disease, and four, glomerulonephritis. Cardiac enlargement and congestive heart failure were present in every one. Infection complicated the course in two. The average creatine figures were 108 mg per cent for the myocardium, 119 for skeletal muscle, and 86 for the diaphragm. The highest single figures for creatine in the diabetic group were 185 mg per cent for voluntary muscle, 107 for the diaphragm, and 212 for heart muscle, although in this case there had been congestive failure. The range of heart muscle creatine in the other five cases was from 65 to 113 mg per cent. Since all were in congestive failure, it is reasonable to expect such low creatine figures for the myocardium. The lowest figures for muscle creatine in all the groups were obtained in the diabetics. It appears that diabetes per se is a factor lowering the creatine reserves of muscle.

The creatine content of the normal diaphragm ranged from 162 to 288, with an average of 234 mg per cent.

Table 3 gives a cross sectional summary of the creatine findings in all the sub-groups and in the normal diaphragm.

DISCUSSION

The rôle of creatine in muscular efficiency has been postulated on well established clinical, experimental and pathological evidence. The more active and more efficient muscles in the body have a higher creatine content. The biological difference between the right and left ventricle is confirmed by different quantities of creatine in each. Diseases of the heart and myocardial infarction result in diminished myocardial creatine, especially marked in the infarcted areas. In failure the creatine of both ventricles is greatly decreased. Diseases affecting one side of the heart show a lower creatine concentration in that side. In the presence of low creatine concentration in the myocardium, heart failure is usually present. In our material creatine concentration of the myocardium was low, not only as the result of heart

failure, but apparently as part of a generalized loss of muscle creatine including the heart, due to chronic and wasting diseases. Nevertheless, even in this material, in congestive failure creatine concentration of all the muscles studied was significantly lower than in the group without failure.

There is a well established creatine-creatinine balance in the body. Creatine excretion for a given individual is a fairly constant quantity. However, increase in creatinine is known to cause an increase in creatine in muscle. The highest figures for creatine in cardiac and skeletal muscle have been reported by Linegar and his co-workers⁵ in cases showing uremia. When creatine saturation exceeded a certain level in skeletal muscle it was then

TABLE III
Average Creatine Values in Cardiac, Skeletal and Diaphragm Muscles in Various Groups

	Group	Number Analyzed	Mg per cent
Cachexial diseases	Heart	8	133
	Skeletal muscle	6	270
	Diaphragm	8	215
Congestive heart failure	Heart	11	106
	Skeletal muscle	6	218
	Diaphragm	8	127
Diabetes (all were in failure)	Heart	6	108
	Skeletal muscle	3	119
	Diaphragm	4	86
Enlarged hearts, no failure	Heart	4	145
	Skeletal muscle	1	395
	Diaphragm	2	197
Hearts weighing 300 gm or less	Heart	8	135
	Skeletal muscle	5	266
	Diaphragm	8	203
Sepsis	Heart	5	170
	Skeletal muscle	2	187
	Diaphragm	4	143
Normal diaphragms		15	234

increased in all muscles, though not uniformly. In uremia plus heart failure, creatine concentration was much less marked. However, like Herrmann and his co-workers,⁷ we did not find marked creatine concentration in the muscle in uremia even when creatinine was greatly elevated in the blood. In the absence of failure the creatine of the muscles was higher than in cases showing failure. This difference may be due to the fact that Linegar and his co-workers⁵ studied a different type of patient. They had only five cases of uremia and six of uremia with congestive heart failure. We had 26 patients with uremia of whom 11 had congestive failure. Their material was derived from young people, ours was chiefly from patients of advanced age with severe chronic diseases.

Evaluation of the entire series shows that hearts in failure had an extremely low average myocardial creatine content, 106 mg per cent, and only one had 212 mg per cent. The enlarged hearts without failure had a slightly higher myocardial creatine content, 145 mg per cent. The myocardial creatine of the diabetics was extremely low, as was to be expected, since they were all in failure, and the average of 108 mg per cent corresponds to the average of the cases in failure. Cachexial diseases yielded an average of 133 mg per cent, but some of these were also in failure. Hearts weighing 300 grams or less had an average myocardial creatine content of 135 mg per cent which may be due to coexistent chronic diseases including malignancies and tuberculosis. Septic cases showed an average myocardial creatine of 170 mg per cent, the highest in the entire series.

Creatine in skeletal muscle showed marked variations. Cachexia, with an average of 270 mg per cent, caused considerable reduction. Congestive failure caused even further reduction to an average of 218 mg per cent. Diabetes plus congestive failure caused a reduction to 119 mg per cent, indicating the rôle of diabetes, per se, in lowering creatine reserves. Sepsis caused a reduction to an average of 187 mg per cent in skeletal muscle.

In cachexias the creatine content of the diaphragm was only slightly decreased, 215 mg per cent, while it was greatly reduced in the myocardium. In congestive failure the creatine of the diaphragm, 127 mg per cent, was markedly decreased. In the diabetics 86 mg per cent were present in the diaphragm. This figure, the lowest for the diaphragm in all the groups, was not surprising since congestive failure and diabetes both played a rôle in decreasing the creatine content. In large hearts without failure the creatine value was 197 mg per cent, a relatively high figure. In sepsis the average creatine of the diaphragm (143 mg per cent), as well as that of skeletal muscle, was particularly reduced, though the heart suffered less. It is evident, therefore, that creatine storage in one muscle system is essentially independent of that in another. However, when creatine reserves were greatly depleted in one system, as in congestive failure and in diabetes with congestive failure, they were also greatly depleted in all other muscle systems.

The low creatine figures in all types of muscle and especially in the left ventricle in heart failure may be due either to greater breakdown of creatine or to inadequate resynthesis of this compound. The increased accumulation of lactic acid in heart failure may prevent the proper resynthesis of creatine and thus contribute to low creatine values and to the continuation and augmentation of heart failure. A low creatine reserve persists in diabetes, as shown in this study and by the work of others,⁵ but it is as yet impossible to determine the responsible factor.

On the basis of Linegar's⁵ work it might have been assumed that the marked nitrogen retention which was present in all our cases would result in creatine retention in all types of muscle. We did not, however, find this to be the case.

The findings presented in this study show a low creatine reserve in cases of creatinine retention associated with uremia. Creatine storage may be depleted or retention offset by congestive heart failure and wasting diseases, despite marked creatinine concentration resulting from uremia.

SUMMARY

1 Creatine determinations were made on the diaphragm, heart and skeletal muscles of 26 patients with uremia. Despite marked creatinine retention associated with uremia the creatine was greatly reduced in all the muscles studied.

2 In uremia associated with chronic congestive heart failure creatine concentration was greatly reduced in all the muscles studied. It appears that congestive failure, diabetes and terminal acute infections cause marked losses of creatine in excess of the possible increase in creatine resulting from creatinine retention. There was no parallelism in creatine loss in heart, diaphragm and voluntary muscles, but when creatine reserves were extremely low in one muscle, they were also greatly reduced in other muscles.

3 Since the lowest figures for the entire series were obtained in the six diabetic patients, who happened also to be in failure, it appears that diabetes is a contributory factor to the reduction of the creatine reserves of all muscles.

4 Patients with enlarged compensated hearts had less marked losses of creatine in heart, diaphragm and skeletal muscles. The loss of creatine reserves appears in these cases to be due to chronic disease, despite the nitrogen retention. The 10 cases with hearts weighing 300 grams or less, and the eight cases of cachectic diseases showed similar findings. The low creatine content in these patients is probably also the result of chronic disease.

5 Creatinine retention in uremia may be expected to cause retention of creatine in muscles and some workers have reported the highest figures for muscle creatine in uremia. Our results, however, do not corroborate these findings.

6 Fifteen normal diaphragms were analyzed. The average creatine content of this muscle was 234 mg per cent. In chronic diseases and congestive failure, especially in diabetes, the concentration of creatine was greatly reduced in the diaphragm as well as in other muscles.

BIBLIOGRAPHY

- 1 MYERS, V. C., and FINE, M. S. The creatine content of muscle under normal conditions. Its relation to the urinary creatinine, *Jr Biol Chem*, 1913, **xiv**, 9.
- 2 DENIS, W. Creatine in human muscle, *Jr Biol Chem*, 1916, **xxvi**, 379.
- 3 CONSTABELL, F. Ueber den Kreatingehalt des menschlichen Herzmuskels bei verschiedenen Krankheitszuständen, *Biochem Ztschr*, 1921, **cxvii**, 152.
- 4 SELOF, D. P., LINEGAR, C. R., and MYERS, V. C. The difference in creatine concentration of the left and right ventricular cardiac muscles, *Arch Int Med*, 1934, **lxxiii**, 574.

- 5 LINGG, C. R., FROST, I. F., and MYERS, V. C. Variation in creatine content of human cardiac and voluntary muscle at autopsy, *Arch. Int. Med.*, 1938, **lxi**, 430.
- 6 COWAN, D. W. The creatine content of the myocardium of normal and abnormal human hearts, *Am. Heart Jr.*, 1934, **ix**, 378.
- 7 HEKMAN, G., DECHERD, G., and OLIVER, T. Creatine changes in heart muscle under various clinical conditions, *Am. Heart Jr.*, 1936, **xii**, 689.
- 8 BOBANSKY, M., and PITCHER, J. F. Clinical significance of the creatine reserve of the human heart, *Arch. Int. Med.*, 1937, **lxv**, 232.
- 9 CHANUTIN, A., and SHARTT, H. A study of creatine metabolism in the nephrectomized white rat, *Jr. Biol. Chem.*, 1929-1930, **lxxxv**, 179.
- 10 BOBANSKY, M. Creatine in human muscle, *Jr. Biol. Chem.*, 1931, **xcv**, 147.
- 11 ROSE, W. C., HEIMER, O. M., and CHANUTIN, A. Modified method for the estimation of total creatinine in small amounts of tissues, *Jr. Biol. Chem.*, 1927, **lxxv**, 543.

OBSERVATIONS ON THE COMPARABLE EFFECTS OF PROTAMINE ZINC AND REGULAR INSULIN IN DIABETIC PATIENTS FOLLOWED OVER A PERIOD OF YEARS *

By ELAINE P RALLI, M D , HAROLD BRANDALEONE, M D , and
HARRY D FEIN, M D , *New York, N Y*

IN a previous study¹ we reported observations on 20 patients with diabetes mellitus who were followed for periods while on regular insulin and who were then transferred to protamine zinc insulin and observed for periods of eight to 14 months. In this group of patients it was found that four never reacted favorably to protamine zinc insulin, and that after eight months five patients had to be returned to regular insulin alone because of the tendency for the occurrence of severe insulin shock or uncontrolled glycosuria. Of the remaining 11 patients of the group eight required both regular and protamine zinc insulin, while three were adequately controlled on protamine zinc insulin alone. Since that report, which was published in 1938, we have continued to observe most of these patients and have studied an additional number of patients. We are now reporting a group of 34 patients who were kept under observation continuously for periods of from one to five years.

During the past five years there have been a great many reports on the use of protamine zinc insulin in diabetes. In a review by Wilder et al.² in 1940, it was pointed out that the most successful use of protamine zinc insulin is in patients with the milder forms of the disease. In contrast to this statement is the opinion of Tolstoi and Weber³ who have treated patients with one large dose of protamine zinc insulin daily and disregarded the degree of glycosuria as long as there were no ketone bodies present in the urine. These two opinions probably represent the extreme views regarding the use of protamine zinc insulin.

We are reporting only patients whom we have observed constantly at regular intervals in the clinics for years. The diets of these individuals were not significantly changed at any time during these observations so that a fair idea of the effect of the protamine zinc insulin therapy, as compared with the effect of regular insulin therapy in a previous period, could be evaluated.

PROCEDURE

These subjects were all patients attending the diabetic clinics of the Third (New York University) Medical Division of Bellevue Hospital or of the New York University College of Medicine Clinic. The patients visited the

* Received for publication June 4, 1941.

From the Diabetic Clinics of the Third (New York University) Medical Division of Bellevue Hospital, and the Diabetic Clinics of the College of Medicine, New York University.

clinic at regular intervals which varied from two to four weeks. All the patients analyzed specimens of urine daily at home and brought such reports to the clinic. A urine analysis was done in the clinic at each visit. If hospitalization was necessary, the patients were hospitalized on the wards of the Third (N. Y. U.) Medical Division of Bellevue Hospital, and any therapy they received was under the direction of the same group of physicians during the period of this study.

In table 1 is given the sex, age and total period of observation of each of the 34 patients. The ages varied from 14 to 81, there were 14 males and 20

TABLE I

Case	Age	Sex	Onset of Diabetes	
			Year	Age
1. L M	46	female	1931	36
2 B S	55	female	1930	44
3 F. K	42	male	1934	35
4 E M	45	male	1933	37
5 M L	39	female	1924	22
6 R R	14	female	1935	8
7 B C	38	female	1931	28
8. S L	28	female	1924	11
9. D M	17	female	1933	10
10 F K	12	male	1928	29
11 J G	21	male	1933	13
12 S C	36	male	1934	19
13 N J	38	male	1929	27
14 S R	75	male	1920	54
15 V K	21	male	1928	8
16 H S	81	female	1923	63
17. M F	51	female	1928	38
18 J K	28	male	1939	26
19 S P	16	female	1936	11½
20 P M	18	female	1939	16
21 E N	31	male	1938	28
22 E P	45	male	1931	35
23 S L	24	female	1935	17
24 M C	41	female	1933	32
25 M S	75	male	1919	53
26 M A	19	female	1937	15
27 E R	25	female	1935	19
28 A A	16	female	1935	10
29 V R	23	female	1936	18
30 A E	62	female	1938	59
31 G G	22	female	1930	11
32 J H	34	female	1939	32
33 S P	31	male	1939	29
34 N D	48	male	1932	39

females. The majority of the patients had had diabetes for about nine years and all but two of them were severe diabetics.

In table 2 the data on these patients, during the periods on regular insulin and during the periods on protamine zinc insulin, are given.

We are not of the opinion that it is absolutely imperative completely to control glycosuria in patients with diabetes, but neither does it seem to us that it is wise to allow unrestricted glycosuria which usually is sooner or later at-

TABLE II

Case	Regular Insulin					Protamine Zinc Insulin					Supplementary Regular Insulin		Remarks
	Diet			Total No Doses	Duration of Treatment in Months	Diet			Total No Units	Total No Doses	Total No Units	Total No Doses	
	C	P	I			C	P	F					
1 L M	200	70	85	4	62	200	70	85	125	2	40	2	Diabetes uncontrolled on protamine insulin 125 u plus 40 regular insulin Returned to regular insulin 50-20-50-30 Diabetes fairly well controlled Weight unchanged
2 B S	250	70	85	4	49	180	65	85	40	1	0	0	Diabetes difficult to control with regular insulin 80 u in four doses Diet cut from C250, P70, F85 to C180, P65, F85 and given protamine insulin 40-0-0 Patient has done well
3 F K	250	70	85	4	5	250	70	85	35	1	30	2	Diabetes fairly well controlled Less hypoglycemic reactions with protamine Weight constant General condition unchanged
4 L M	200	75	85	4	5	200	65	85	20	1	60	2	Insulin now given twice daily but requires three injections, two regular and one protamine Diabetes not controlled any better than on regular insulin Weight increase 10 pounds Mild glycosuria
5 M L	200 300	75 75	85 85	4 2	45	300	75	85	40	1	35	1	Control of diabetes good for four years The patient gained 10 pounds, general condition improved The patient then began to experience shocks alternating with glycosuria The protamine was reduced finally to 15 u, the time of administration changed to noon Finally the protamine was discontinued and the patient was given 55 u of regular insulin daily in two doses, and on this she was well controlled Patient on protamine plus regular insulin for nine mos Uncontrolled with numerous severe insulin shocks Returned to regular insulin in three doses (80 u), no shocks Gained 31 pounds in 26 mos Protamine no advantage
6 R R	250	75	85	3 2	15	320	75	95	25	1	15	2	

TABLE II (Continued)

Case	Regular Insulin						Protamine Zinc Insulin						Supplement by Regular Insulin		Remarks
	Diet			Total No Units	Total No Doses	Duration of Treatment in Months	Diet			Total No Units	Total No Doses	Duration of Protamine in Months	Total No Units	Total No Doses	
	C	P	F				C	P	F						
	C	P	F	C	P	F									
7 B C	200	75	85	50	3	37	250	75	85	35	1	51	15	1	Controlled on regular insulin but controlled 13 well on protamine and number of doses decreased to one a day. Gain of five pounds in three weeks (not overweight)
8 S I	200	65	85	75	4	36	200	75	85	30	1	10	20	2	Patient not controlled on protamine. Changed to regular insulin 15-8-10-5. Diet C-180-65-120. At present general condition not good. Pt does not care for self properly. Glycosuria and insulin shocks, minimal. Husband has severe pulmonary tuberculosis which the patient has now developed
9 D M	300	75	85	60	3	28	300	75	85	30	2	16	40	2	Patient uncontrolled on protamine plus regular insulin. Was changed to regular insulin 35-0-25 with diet C250 P75 F85, and is now improved
10 F K	250	75	85	50	3	45	250	75	85	50	1	56	10	1	Patient improved on protamine. Has pernicious anemia, weight unchanged
11 J G	350	75	85	100	4	31	350	75	85	10	2	62	20	2	Well controlled. Improved. Gained weight
12 S C	300	75	85	110 115	4 4	36 36	380	70	95	90 40	2 1	21	40 75	2 3	Poorly controlled on protamine which was discontinued after 21 mos. Fairly well controlled on regular alone for 36 mos. Began again on one dose of protamine and three of regular
13 N J	200	65	85	65	4	72	200	65	85	53 20	2 1	6 44	0 45	0 2	Patient experienced more insulin shocks on protamine than on regular. His diabetes was somewhat difficult to control as it was complicated by numerous rectal infections. After six mos. protamine was discontinued for about six mos. and then started again in combination with regular insulin. On this combination he is fairly well controlled

TABLE II (Continued)

Case	Regular Insulin					Protamine Zinc Insulin						Supplementary Regular Insulin		Remarks
	Diet			Duration of Treatment in Months	Total No Units	Total No Doses	Diet			Total No Units	Total No Doses			
	C	P	F				C	P	F					
14 S R	250	65	85	48	65	4	300	65	85	1	2	20	1	Patient in hospital for two mos , could not control diabetes Frequent and severe shocks Returned to regular insulin with control of diabetes, 20-0-20-5
15 A K	250	65	85	53	85	4	250	65	85	2	1	20	1	Had several admissions to hospital for ketosis Impaired liver function with hepatomegaly Protamine discontinued Controlled on regular insulin 35-0-25
16 H S	150	65	85	72	10	1	150	65	85	1 25	1 1	15 0	1 0	Patient was controlled on regular insulin, but because she was unable to take insulin herself she was switched to protamine which could be given once daily by a nurse Controlled on 25 u protamine alone now
17 M F	150	65	85	36	32	2	150	65	85	1	25	5	1	Diabetes discovered in 1931 Remained untreated until 1936 Weight unchanged on regular or protamine insulin Diabetes controlled equally as well Takes insulin only once daily
18 J K	250	65	85	10	80	2-3	250	65	85	1	2	15	1	Patient was started on 20-0-0 protamine and 15-0-0 regular, but was not controlled and developed persistent and increasing acetone Changed to regular insulin 40-0-40 Control moderate.
19 S P	250	90	75	12	50	2	300	90	75	1	9	10	1	Patient came to clinic with 40-0-0 protamine and 0-0-10 regular Glycosuria uncontrolled, insulin rearranged to 40-0-25 protamine Gained 10 pounds Not entirely controlled Returned to regular insulin alone, two doses daily Well controlled

TABLE II (Continued)

Case	Regular Insulin						Protamine Zinc Insulin						Supplementary Regular Insulin		Remarks
	Diet			Total No. Units	Total No. Doses	Duration of Treatment in Months	Diet			Total No. Units	Total No. Doses	Duration of Protamine in Months	Total No. Units	Total No. Doses	
	C	P	F				C	P	F						
20 P M				Never on regular alone			250	70	85	20	1	20	20	1	Patient started on protamine 15-0-0 upon discovery of diabetes. Lost weight, increasing glycosuria. Insulin raised to protamine 20-0-0, regular 20-0-0. Finally controlled on regular and protamine.
21 E N				Never on regular alone			350	70	85	30	1	27	50	2	Patient did not adhere to diet. At first controlled on protamine alone. Now requires protamine and regular.
22 E P	175	75	85	45	2	72	175	75	85	50	1	20	0	0	Patient was controlled on regular insulin 25-0-20, but changed to protamine 50-0-0 and continues well controlled.
23 S L	200	75	85	45 45	2 3	22 12	230	75	85	15	1	18	15	1	Not well controlled on regular insulin. Changed to reg. 15-0-0, protamine 15-0-0, and is moderately controlled. Patient not very cooperative. Returned in March 1940 to regular alone. Was pregnant and delivered a normal child during the past year.
24 M C	180	75	85	70	3	24	150	65	85	30	1	31	15	1	Patient better controlled on protamine insulin 30-0-0 and regular insulin 15-0-0 than on regular 30-10-30.
25 M S	150	65	85	50	3	2	150	65	85	40	1	13	0	0	Patient improved on protamine. Diabetes fairly well controlled. Fewer injections.
26 M A	300	65	85	55-70	3	24	300	65	85	40 25	1 2	22 7	0 20	0 2	Patient started on protamine and kept on it for ten months. Became difficult to control. Changed to regular insulin and continued on it for 2½ months but was inadequately controlled with the development of her menses. Began again on protamine as a supplement to regular insulin and carried on this seven months. Controlled fair on this combination.
27 E R	200	65	85	100	4	7	200	65	85	25	1	18	65	2	Patient always difficult to control. Started on regular insulin and fairly well controlled. Because of frequent injections changed to protamine and regular. Patient fairly well controlled.

TABLE II (Continued)

Case	Regular Insulin						Protamine Zinc Insulin						Supplementary Regular Insulin		Remarks
	Diet			Total No Units	Total No Doses	Duration of Treatment in Months	Diet			Total No Units	Total No Doses	Duration of Protamine in Months	Total No Units	Total No Doses	
	C	P	F				C	P	F						
28 A V	230	85	55	4	3	180	65	85	2	80	2	19	40	1	Patient fairly well controlled on four doses of regular insulin. Changed to protamine and regular in two doses. Fairly well controlled. In Jan 1941 stopped regular insulin. Now on two doses of protamine
29 A R	175	75	85	1	13	175	75	85	1	8	1	36	45	2	Patient on four doses of regular insulin fairly well controlled. Placed on two doses with one dose protamine. Well controlled. B M R +36
30 A E				None		150	75	85	1	15	1	12	0	0	This patient was never on regular insulin. She was at first given protamine insulin alone. This was cut to 10 u and she was well controlled. Finally insulin was omitted altogether and she continued to be sugar-free. This is a very mild diabetic and probably would have done equally well on regular insulin
31 G G	150	65	70	3	37				2	40	2	60	40	2	Patient controlled first on regular insulin. Then transferred to regular and protamine, and has been well controlled on dose stated
32 I H	280	90	90	1	16	200	70	75	1	10	1	7	0	0	This patient developed diabetes during her first pregnancy. She was never difficult to control and she was carried on protamine insulin for seven mos but noted a tendency to insulin reaction. She was changed to regular insulin, the same dose, had no reactions and said she felt better. The dose of insulin is now reduced to 8 units of regular
33 S P	275	80	95	2	2	314	80	95	1	25	1	22	20	2	When this patient was regulated on regular insulin he was changed to regular and protamine. For nine mos he required only one dose of regular, but since then has required two doses to supplement the one dose of protamine
34 M D	200	65	90	2	70				1	15	1	34	25	2	This patient is fairly well controlled on this regimen. He was transferred to protamine because two doses of regular insulin were not enough to control his diabetes

tended by loss of weight and a tendency to ketosis. In this group our effort was to keep each patient moderately sugar-free, to maintain his body weight, and to provide him with a diet that was adequate for his daily needs. Insulin was given in sufficient doses to accomplish these results.

In discussing the effects of protamine zinc and regular insulin on this group of patients, the criteria that we have used to indicate improvement on protamine zinc insulin are, (1) a smaller number of injections daily, (2) improvement in the general clinical condition of the patient, such as gain in weight, (3) a decrease in the number of units of insulin required daily.

Analysis of the cases reported in table 2 shows that nine of them (1, 6, 8, 9, 12, 14, 15, 18 and 19) did not improve with protamine zinc insulin, and in fact did poorly on it so that they were returned to regular insulin alone. Six of the nine cases who did not do well on protamine zinc insulin were kept on this insulin for periods varying from 9 to 21 months. The other three were given a trial in the hospital for periods of one or two months. The difficulty in most of these cases was severe insulin shock. This occurred regardless of the time the protamine zinc insulin was given and was severe enough to cause unconsciousness. The other most annoying symptom was intense headache.

The course of the diabetes in these nine cases since their return to regular insulin has been observed for periods varying from 10 to 62 months. Two of these patients (cases 1 and 18) are not well controlled on regular insulin. These patients are not cooperative, and it is impossible properly to evaluate the effect of either type of insulin. One patient (case 9) has developed tuberculosis and this has somewhat influenced her insulin requirement, but while under our observation she was well controlled on regular insulin. The other six patients have been controlled on regular insulin. In case 12 numerous adjustments of the dose of insulin have been required as the patient is going through the period of adolescence, and under these circumstances it is quite usual for the insulin requirement to vary somewhat. Four patients (cases 4, 13, 23, and 32) did no better on protamine zinc insulin than they had done on regular insulin. One patient (case 5) did well on protamine zinc insulin alone for almost four years but then became difficult to control and was finally returned to regular insulin. This disposes of 14 of the cases studied.

The other 20 patients may be considered to have done better on a combination of protamine zinc insulin and regular insulin than on regular insulin alone and among these some did much better than others. Examples of those who did really well on protamine zinc insulin were Case 2 in which four doses of regular insulin were required daily, for the past 56 months one dose of protamine zinc insulin has sufficed. Case 7, which showed good control by regular insulin, but on protamine zinc and regular insulin the patient needs to take insulin only once daily in two injections. Case 10, in which pernicious anemia was a complication. The patient required regular

insulin three times a day, but now takes one dose of regular and one of protamine zinc insulin and is well controlled Case 11, in which the requirement was four doses of regular insulin daily The patient is now controlled on protamine zinc and regular insulin given twice a day Case 16, in which control is now maintained by protamine zinc insulin alone Cases 20 and 21, patients who were never treated with regular insulin alone but who have

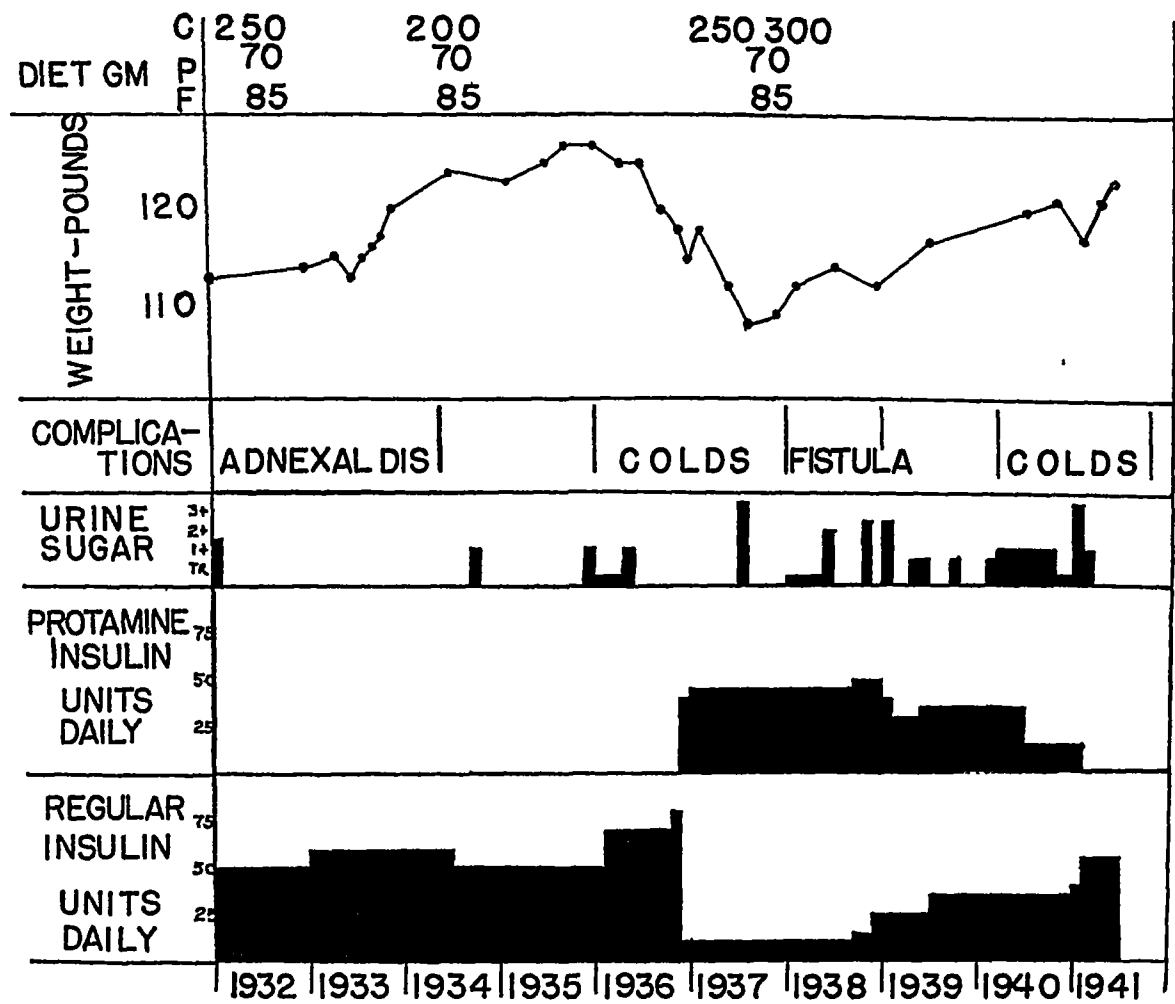


CHART 1 Graphic representation of the course of diabetes mellitus in Case 5 while being treated with regular insulin and while under protamine zinc insulin therapy

done well on a combination of protamine zinc and regular insulin Case 22, in which two doses of regular insulin were formerly required and the diabetes now is controlled on one dose of protamine zinc insulin Case 24, in which the patient is better controlled on the combination of protamine zinc and regular insulin than she was on regular insulin alone Cases 25 and 28 which demonstrate control by fewer injections of protamine zinc insulin alone Case 30, satisfactory continued treatment by protamine zinc insulin alone Case 31, improved control by protamine zinc and regular insulin as compared with regular insulin alone Case 33 in which the patient has done well on protamine zinc and regular insulin

Of these 20 cases six have been well controlled on protamine zinc insulin alone. The rest have required combinations of protamine zinc and regular insulin.

DISCUSSION

From this group of 34 patients, most of whom have been under observation for an average of four and one-half years, one gets a fair idea of the course of diabetes as influenced by regular and protamine zinc insulin. The cases that showed the most striking improvement on protamine zinc insulin are those that can be handled with one dose of the latter daily. This obviously is much more convenient for the patient. In the majority of the cases, however, it is apparent that protamine zinc insulin alone is not sufficient to control the glycosuria, and it becomes necessary to use a combination of protamine zinc and regular insulin. In some of these cases this combination is an improvement on the use of regular insulin alone, in others the control of the diabetes is no better on the combination than on the regular insulin alone. In the latter event one wonders whether there is any point in using protamine zinc insulin.

Some cases apparently do not respond well to the use of protamine zinc insulin. These patients are almost invariably severe diabetics and often may not be well controlled on regular insulin, due to a lack of cooperation on the part of the patient.

In using protamine zinc insulin in the treatment of diabetes some patients will respond better than others, and it is interesting to note that some patients do very well on protamine zinc insulin for a period of years and then for some reason or other seem to require more regular insulin, or protamine zinc insulin has to be abandoned altogether. It is possible that this is due to lack of absorption of the protamine zinc insulin. Many patients have complained that they have found it increasingly difficult to find a place to inject protamine zinc insulin after this insulin has been used for years.

As a result of our observations over the past six years it is our policy to try patients on a combination of protamine zinc and regular insulin, arranged in such a way that the patient will not have to take insulin more than twice daily. Our effort is to reduce the number of doses to a minimum which will control the patient's diabetes sufficiently well so that he does not lose weight and is capable of doing his work. In cases where patients have required frequent doses of regular insulin we have endeavored to use the combination of protamine zinc and regular insulin and, as the results show in these 34 cases, this has been possible in about 60 per cent of the cases. We have learned also that in using protamine zinc insulin one must adjust it to the needs of the particular patient. It is our impression that not more than 40 units should be given in one dose. It seems as if larger doses than this are not correspondingly effective. One of the most effective methods of using protamine zinc insulin is in patients who have previously required a

dose of regular insulin late at night in order to remain sugar-free through the night. In such cases, as pointed out also by Martin et al,⁴ by giving a dose of protamine zinc insulin at supper time the glycosuria which occurs at night, and often is the cause of nocturia, is avoided.

Several of the patients in this study were hospitalized at times because of some intercurrent infection. During the period of infection it was observed that the patients did better on regular insulin alone than on combinations of regular and protamine zinc insulin. Two outstanding examples were cases 2 and 13. In case 2 the patient suffered from chronic gall-bladder disease and during acute attacks which required hospitalization it was found necessary to treat her with regular insulin every two hours to control the glycosuria and the ketosis. In case 13 recurrent rectal abscesses raised the patient's insulin requirement and it was necessary to give him regular insulin every three hours during the acute period to prevent ketosis and control the glycosuria. It is our feeling that during the period of an acute infection it is wiser to use regular insulin alone as it is easier to control the glycosuria, and as the infection subsides there is no danger of insulin shock as from an overdose of protamine zinc insulin.

Some of the divergence of opinion as to the efficacy of protamine zinc insulin in the treatment of diabetes possibly results from the fact that the patients have not been under observation for a sufficient period of time, and often are not seen by the same observer during varying periods of the disease. The fact that the diabetic patient is well controlled on protamine zinc insulin for some time and then goes through a period in which he does not respond so well may be due to several factors. First among these may be poor absorption of the protamine zinc insulin. Second may be the occurrence of intercurrent infections which always tend to increase the severity of the diabetes. Third is the possibility that the patient may not be adhering to his diet. It has seemed to us that the best policy is to adjust the insulin, whether it is protamine zinc or regular insulin, to the patient's needs. It does not seem to us that one can assume too dogmatic a point of view, as it is obvious that when the diabetic patient is observed for a sufficiently long period there will be times when his insulin requirement will change, and at these times it also seems that the type of insulin best suited to his needs may change. On the whole, the most efficient method of using protamine zinc insulin is as a supplement to regular insulin. Its more prolonged action makes it possible in some cases to omit the midday and night injections of regular insulin, and this action also tends to stabilize the patient's carbohydrate metabolism.

SUMMARY

A group of 34 diabetic patients observed on both regular and protamine zinc insulin is reported. The average period of observation was four and one-half years. Of these patients, six were well controlled on protamine zinc

insulin alone, 14 did better on combinations of protamine zinc and regular insulin than on regular insulin alone. Treatment with protamine zinc insulin was ineffective with nine of the patients and they were returned to regular insulin alone, on which they were controlled. Four patients did as well on regular insulin alone as they did on combinations of protamine zinc and regular insulin. One patient who had been treated with protamine zinc insulin alone for almost four years became impossible to control and it was necessary to return her to regular insulin.

It is felt that a combination of protamine zinc and regular insulin is an effective way of controlling glycosuria in the diabetic patient, but it is important to realize that such procedure may have to be altered during periods of acute infection.

REFERENCES

- 1 RATH, ELAINE P, FEIN, HARRY D and LOVITLOCK, FRANCIS J. Observations on the continued use of protamine zinc insulin in patients with severe diabetes mellitus, *Am J Med Sci*, 1938, **cxcvi**, 28
- 2 WILDER, R. M., BROWN, H. C., and BUTT, H. R. Diseases of metabolism and nutrition, *Arch Int Med*, 1940, **lxx**, 39
- 3 TOISTOL, E., and WILDER, F. C. Protamine zinc insulin, a clinical study, *Arch Int Med*, 1940, **lxxi**, 670
- 4 MARTIN, H., DRURY, D. R., and STROUS, S. Basal requirement in diabetes mellitus, *Arch Int Med*, 1940, **lxxi**, 78

CONVULSIONS IN PAGET'S DISEASE; ELECTRO-ENCEPHALOGRAPHIC OBSERVATIONS ⁺

By JOSEPH A. MUFSON, M D , and PAUL CHODOFF, M D ,
New York, N Y

RECENT electroencephalographic studies have thrown new light on the question of hereditary factors in epilepsy. Evidence has been presented which not only substantiates the long accepted view as to the importance of heredity in idiopathic epilepsy but also tends to break down the distinction which until now has divided convulsive states into idiopathic and symptomatic varieties. Strauss, Rahm, and Barrera,¹ and Lowenbach² have demonstrated an increased occurrence of cerebral dysrhythmia among supposedly normal relatives of epileptics. Lennox, Gibbs and Gibbs³ obtained abnormal tracings in 60 per cent of the relatives of 94 patients with convulsions and cerebral dysrhythmia, and found that dysrhythmia occurred as frequently among the relatives of patients with symptomatic epilepsy as among relatives with the idiopathic variety. In a control group of 100 persons who had no near relatives with epilepsy, 10 per cent had abnormal records. These workers have concluded that cerebral dysrhythmia represents visible evidence of a constitutional predisposition to epilepsy or some allied disorder, and that the dysrhythmia of epilepsy is inheritable.

Recently two patients with convulsive seizures beginning late in life came under our observation. Both were found to have osteitis deformans with involvement of the skull. Careful study failed to reveal in either case any other associated disease which could account for the seizures. The occurrence of convulsions in the son of one of the patients led us to investigate the electroencephalographic findings in these patients, in five other cases of Paget's disease in the hospital, and in all available near relatives.

INTERPRETATION OF ELECTROENCEPHALOGRAPHIC RECORDS

The electroencephalographic abnormalities which have been found in cases of epilepsy may be considered in regard to first, the spontaneous tracing, and second, the effects of hyperventilation. Gibbs and Gibbs⁴ feel that the occurrence of alternating slow wave and spike activity is diagnostic of petit mal and that there is a definite difference between petit and grand mal tracings, the latter being marked by the occurrence of abnormally slow or fast waves in interseizure periods. The "crescendo burst of fast waves" which they find during actual grand mal seizures are rare in their interseizure

⁺ Received for publication August 9, 1941.

From the Neurophysiology and Neurological Divisions, Montefiore Hospital, New York.
Work done with the assistance of the Frances and John L. Loeb Foundation in memory of Arthur Lehman.

records. They consider findings during hyperventilation as of limited value in the electroencephalographic diagnosis of epilepsy.

In this laboratory, experience with a large number of clinically diagnosed epileptics has shown that the occurrence of bursts of high amplitude slow waves without preceding gradual slowing, usually of a 3 per second frequency and with or without interspersed spikes, is also a characteristic feature of the convulsive state whether of the petit or grand mal type. It is further felt that on the basis of comparison with many normal controls, the appearance of such waves during or after measured periods of deep over-ventilation (180 seconds) is of definite diagnostic significance in epilepsy.

In the records discussed in this paper, both the spontaneous and hyperventilation portions were carefully examined for any of the above mentioned abnormalities.

CASE REPORTS

Case 1 S. G. a 45-year-old white man, was admitted to Montefiore Hospital on July 31, 1940, complaining of episodes of unconsciousness of six years' duration. His health had been excellent up to the onset of his present illness. He was married and had one child, a five year old son, who on two occasions in the past two years had been observed to have attacks of generalized twitchings with unconsciousness. The boy was receiving daily phenobarbital medication. The patient's wife had never had a convulsion and there was no other history of epilepsy, migraine, chorea, or allied disorders in the family. There was no background of alcoholism. Three months before his first convulsion the patient was in a brawl and was beaten about the nose and eyes. His face was discolored but there was no loss of consciousness and no confusion. There were no headaches or dizziness following this episode and no apparent disability. The first seizure consisted of a two minute period of unconsciousness. Since that time, he has had repeated attacks occurring at intervals of 30 to 90 days, with their frequency increasing during the past two years. There is no aura preceding the seizure, which may occur either during the day or night. In the attacks which have been observed recently the body becomes rigidly arched and the face twitches. At times there is biting of the tongue and drooling of saliva. Neither generalized nor local clonic movements have been observed.

Physical Examination The patient was a short, rather plethoric white man who did not appear ill. His head was somewhat enlarged but not unduly so. His hat size had increased from 7 $\frac{1}{2}$ to 7 $\frac{3}{4}$ in the past year. General examination revealed no abnormalities and the neurological status was completely negative. Carotid sinus pressure had no perceptible effect.

Laboratory Data A roentgenogram of the skull revealed numerous circular areas of bone condensation in the fronto-parietal region. The appearance was typical of osteitis deformans. In roentgenograms of the pelvis there was marked bone condensation in the right sacro-iliac synchondrosis also considered to be due to Paget's disease. On August 11, 1940, an air encephalogram was made and revealed only slight dilatation of the lateral and third ventricles. Blood phosphatase level was 31 Bodansky units (normal level 4 to 6 units). Blood calcium and phosphorus were within normal limits. The glucose tolerance test was normal. There were no abnormalities of the spinal fluid.

Electroencephalography (Figure 1) In the spontaneous record the predominant alpha activity was of 10 per second frequency, the beta of 18-24 per second. In addition, there were low voltage slow waves and fast spike activity appearing in

bursts During four hyperventilations, the patient developed outbursts of high amplitude, three per second waves in all leads These continued to appear for some time after cessation of over-ventilation

Case 2 N L, a 63-year-old white salesman, was admitted to Montefiore Hospital on February 16, 1941 because of fainting spells of six months' duration His birth and early life were uneventful except for constant headaches between the ages

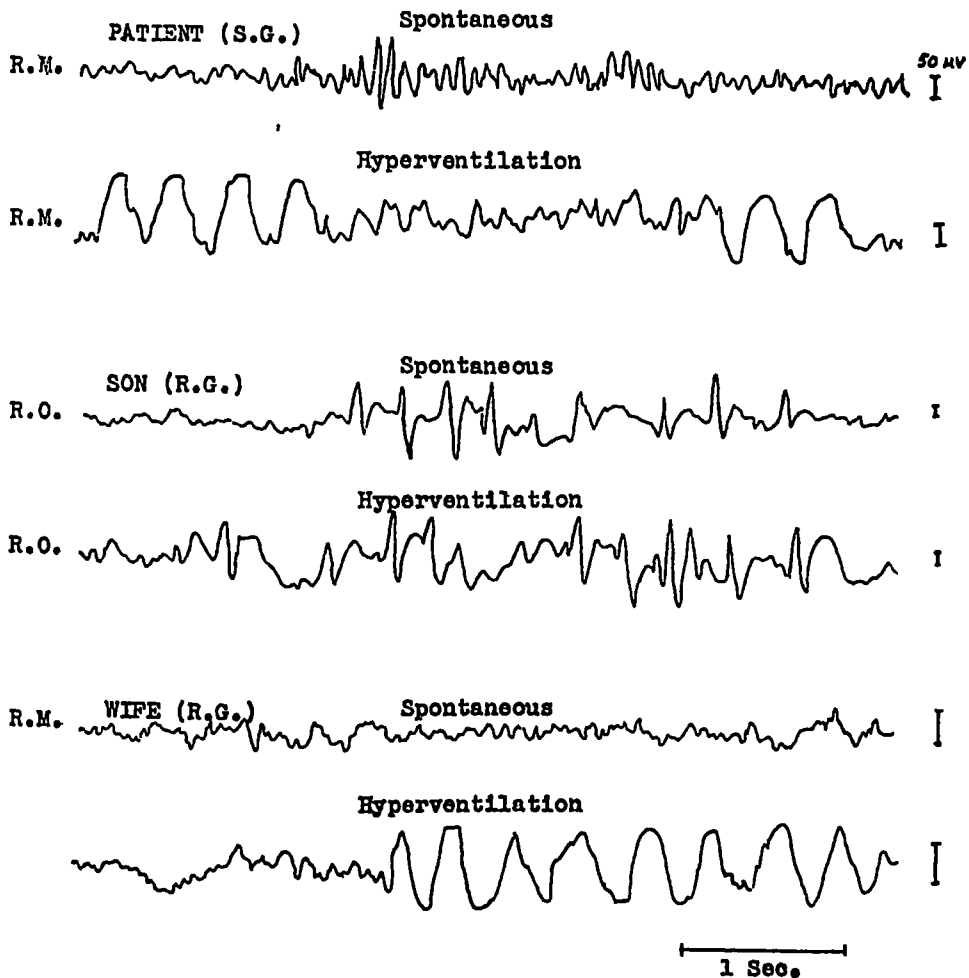


FIG 1 Tracings from patient, S G, son, and wife The spontaneous record of the patient shows an abrupt transition from normal to high amplitude, spike activity The hyperventilation record shows two outbursts of high amplitude, three per second waves with suggestive spike formation in the first Typical wave and spike configurations are shown in both the spontaneous and hyperventilation records of the patient's son who has clinical epilepsy The spontaneous record of the patient's wife shows slight disorganization In the hyperventilation record is shown a prolonged burst of high amplitude, three per second waves

of 10 and 14 which necessitated his leaving school At 14, the headaches ceased spontaneously and did not recur until the present illness Beginning at the age of 30, the patient noticed a gradual and progressive increase in the size of his head At the age of 30 his hat size was $7\frac{1}{2}$, at present a size $8\frac{3}{4}$ is too small for his head The changes have been more pronounced during the past year For the past 20 years, there has been a gradual diminution in hearing in the left ear Four months before admission he developed progressive loss of hearing in the right ear so that at present he is almost totally deaf After 1932, he noticed a decrease in visual acuity His present complaints date back to six months before admission when he developed

attacks of dizziness and fainting spells occurring about once every three to four weeks. Each attack of syncope came on during the day while the patient was walking on the street and was preceded by several minutes of dizziness during which surrounding objects seemed to move about him. He would then suddenly lapse into unconsciousness for a period of two to three minutes. Upon awakening, there was complete amnesia for the event. At times, the entire attack consisted only of the prodromal vertigo. Coincident with the fainting spells the patient developed "shooting pains" in the temples which radiated posteriorly to the occiput. Five months before admission, he noted the onset of dull aching pains in his knees, hips, elbows, thighs, and back. In addition to the fainting spells which have been described the patient had one generalized convulsive seizure in his home on Thanksgiving Day, 1940. There was no vertigo preceding this attack. According to his wife, who witnessed the seizure, there were involuntary clonic movements involving the face and all extremities. There was no frothing at the mouth and no incontinence. He was unconscious for a period of two to three minutes.

Physical Examination The patient was a tall, well-developed white man in no acute distress. The head was markedly enlarged and presented prominent parietal bosses. The circumference was 66 centimeters. The heart was slightly enlarged to the left. Blood pressure was 118 systolic and 80 diastolic. The pulse rate was 68 per minute and auricular fibrillation was present. There was a systolic apical murmur. The peripheral vessels were moderately sclerotic. Carotid sinus stimulation produced no demonstrable effect.

Neurological Examination The tendon reflexes in the upper extremities were hypoaactive. There was a defective plantar response on the left but no pathological reflexes. Smell was impaired bilaterally, right more than the left. There was a right divergent strabismus with crossed diplopia on looking to the right. Vision in the right eye was reduced to 10%, the right visual field showed an irregular constriction. The right optic nerve head appeared lemon-yellow in color. There was evidence of retinal arteriosclerosis. Hearing was markedly impaired bilaterally with almost complete deafness on the left. There was diminution of both bone and air conduction. The audiometer test revealed marked impairment of perception of the higher notes indicating bilateral nerve deafness.

Laboratory Data The urine and blood count were normal. Blood phosphatase level was 55 Bodansky units. A spinal tap revealed an initial pressure of 153 mm of fluid with normal manometric alterations on test. The total protein was 51 mg per cent. Blood and spinal fluid serology were negative. An electrocardiogram showed left axis deviation and auricular fibrillation. Caloric testing showed complete absence of response on the right and slight response on the left. Roentgenograms of the skull, spine, and pelvis revealed bony changes typical of Paget's disease.

Electroencephalography (Figure 2) In the spontaneous record there was very little alpha activity and this was of 12 per second frequency. There was a large amount of beta activity. In some places, waves of increased amplitude suggestive of spikes, and irregular slow waves of varying amplitude and frequency appeared. Both during and after hyperventilation, there were outbursts in all leads of high amplitude three per second waves.

COMMENT

A review of the literature reveals that convulsions are not a common accompaniment of osteitis deformans. In his original description in 1876, Sir James Paget⁶ expressed surprise that "the mind remains unaffected even when the skull is hugely thickened." Marie⁷ describes a case exhibiting

fugues, epileptic attacks, and diabetes insipidus. In addition to having osseous disease this patient was a chronic alcoholic. Cahane and Cahane⁸ report a case of epilepsy associated with Paget's disease occurring in a young woman. In a series of 34 cases of osteitis deformans with neuropsychiatric complications Kay, Simpson, and Riddoch⁹ describe one with generalized convulsive seizures. Kasabach and Gutman,¹⁰ writing on osteoporosis circumscripta, which they consider a variant of osteitis deformans, report out of 20 cases one in which generalized convulsions occurred. Grunthal¹¹ and Nonne¹² state that epileptic attacks occur in Paget's disease but give no examples in their own material. Many other reports on the neuropsychiatric complications of this disease (Wyllie,¹³ Gregg,¹⁴ Schwarz and Reback,¹⁵ Moynan,¹⁶ and Kaufman¹⁷), although describing cranial nerve involvement, cord compression, and mental changes, do not mention convulsions as a symptom. Gutman and Kasabach,¹⁸ in an analysis of 116 cases, and Sugarbaker,¹⁹ in 51 cases, do not report convulsions.

Since cranial osteitis deformans does not cause convulsions in a majority of cases, how then are we to explain the occurrence of seizures in some cases of this disease in which there is no other adequate explanation? The work of Lennox, Gibbs and Gibbs³ suggests that epilepsy, both the "idiopathic" and the so-called "symptomatic" varieties, rarely occurs without an inherited predisposition. In both our cases convulsive seizures began long past the usual age of onset of idiopathic epilepsy, and in neither of them is there any evidence of focal brain disease. Electroencephalographic tracings reveal in both the diffuse cerebral dysrhythmia seen in epilepsy and allied conditions. It may be that the postulated inherited predisposition in these patients is of such low intensity that under ordinary circumstances their lives might have been passed without clinical expression of their epileptic tendency. It required the intervention of a precipitating factor, in this case Paget's disease, to allow the convulsive explosion to break through.

In order to further investigate the validity of this hypothesis of hereditary predisposition, electroencephalographic tracings were obtained of the available near relatives of our two patients. The only child of S. G. (case 1) is of particular interest since he is known to have had two episodes of generalized twitchings with loss of consciousness. The record of this boy revealed frequent spontaneous outbursts in all leads of three per second waves and spike formations (figure 1). For the sake of completeness a record was obtained of the child's apparently normal mother, the wife of S. G. Although the spontaneous record was within normal limits, both during and after hyperventilation there were outbursts of high amplitude, three per second waves (figure 1). The three members of this family thus provide a cogent example of the different ways in which hereditary predisposition and precipitating factors may interact. In the case of S. G. an inherited predisposition plus an exogenous factor resulted in clinical epilepsy. His wife, with a probable mild predisposition and no exciting cause, escaped overt

manifestations. The child of this union, the victim of a double inheritance, developed frank epilepsy early in life.

The two children of N. L. (case 2), neither exhibiting clinical evidence of epilepsy, were also subjected to electroencephalography (figure 2). The record of the daughter, aged 35, showed some spontaneous slow waves and an alternating fast and slow rhythm. During hyperventilation there ap-

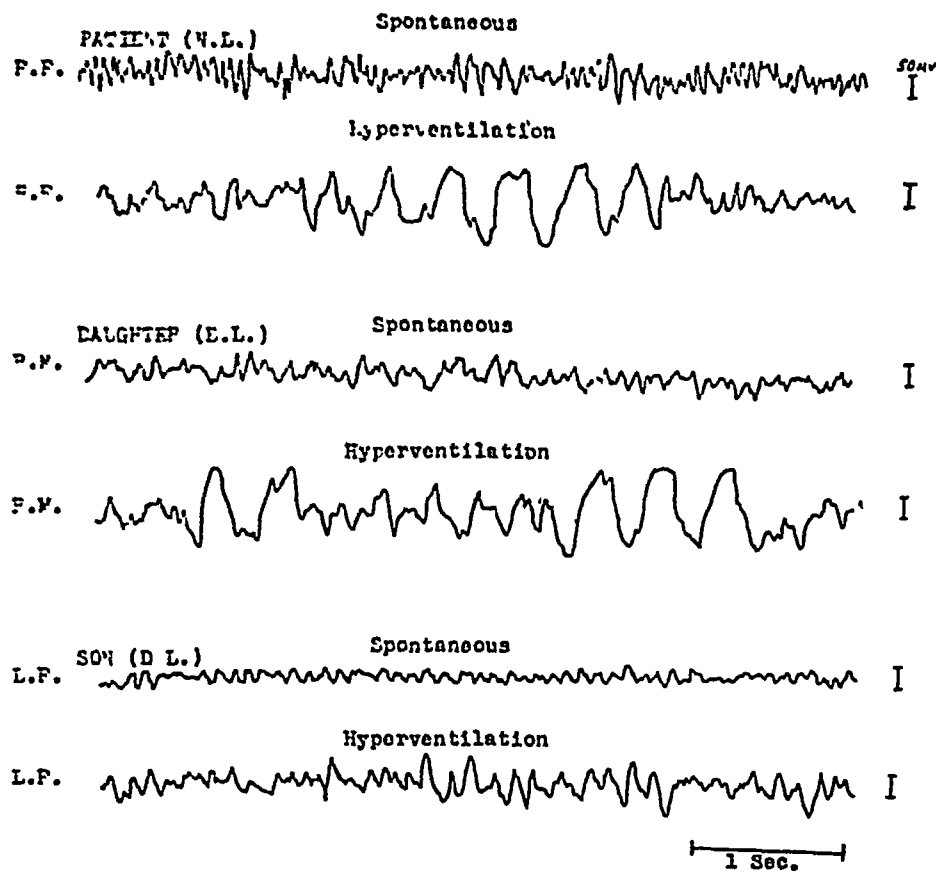


FIG 2 Tracings from patient, N. L., daughter, and son. The patient's spontaneous record shows disorganization with waves of increased amplitude suggestive of spikes and some irregular, slow activity. During hyperventilation, an outburst of high amplitude, slow waves is shown. The spontaneous record of the daughter shows abnormal slow activity. In the hyperventilation record an outburst of high amplitude, slow waves is illustrated. Such outbursts, however, were relatively infrequent during the over-ventilation period. The spontaneous record of the son is normal. The maximum change occurring after 180 seconds of hyperventilation is shown.

peared a few bursts of high voltage three per second waves in all leads. The tracing of the son, aged 31, was within normal limits. In this family, the daughter's borderline record may or may not be evidence of a transmissible factor.

To eliminate the possibility that cranial osteitis deformans per se may produce a diffuse cerebral dysrhythmia, electroencephalographic records were obtained on five other cases of Paget's disease present in the hospital for various non-neurological complaints including cardiac decompensation, frac-

ture of the femur, and one with syphilis and optic neuritis. The ages of four of the five ranged from 58 to 84, the fifth was 40 years old. In none was there a personal or family history of convulsions. The tracings displayed such abnormalities as slowing of alpha activity, and inconstant slow waves of four to seven per second frequency not appearing in all leads. The patient with optic atrophy of the right eye showed alpha activity of increased amplitude on the right side, and numerous slow waves of six to seven per second frequency originating from the right occipital region. Neither

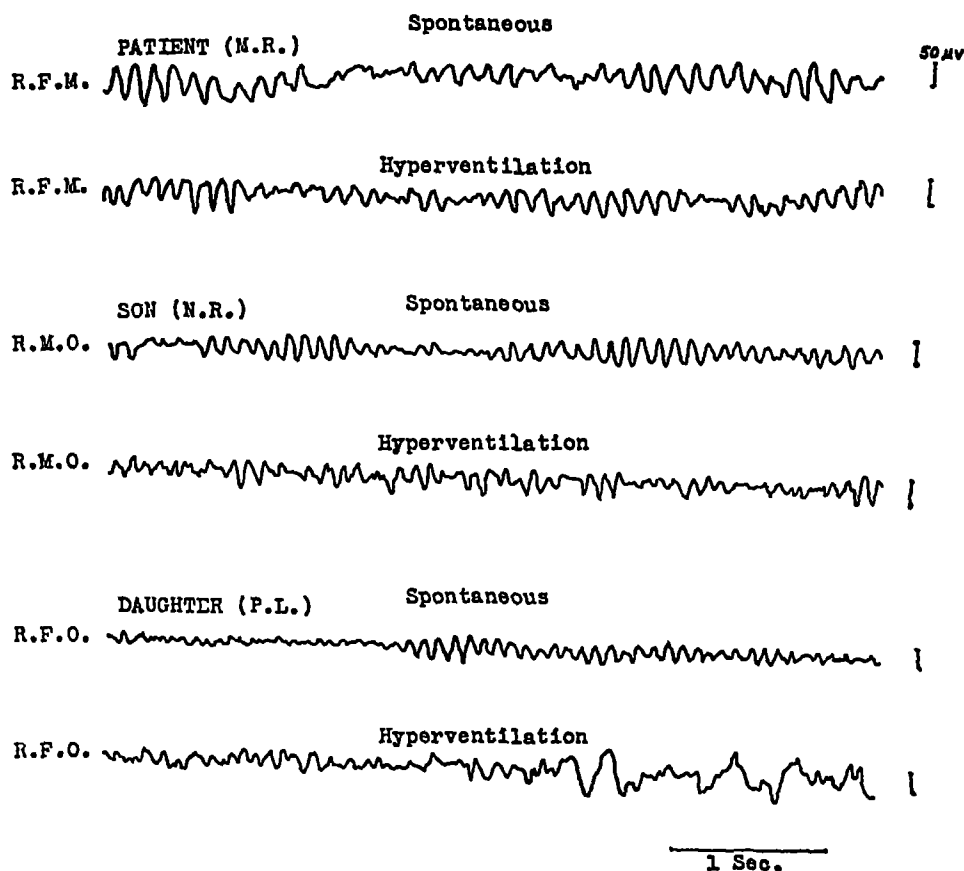


FIG 3 Tracings from one of the five cases of Paget's disease without convulsions, and from his son and daughter. All spontaneous records are normal. In the records of the patient and his son there is very little change during hyperventilation, in the daughter's record, only the gradual development of irregular, slow activity is shown.

spontaneously nor during hyperventilation did any of these tracings remotely resemble a diffuse cerebral dysrhythmia. Hyperventilation, in contrast to the first group of cases, while causing some gradual slowing, failed to produce outbursts of three per second waves (figure 3). The records of four children of two of the patients in this latter group were obtained and all were within normal limits.

Although no final conclusions can be drawn from a series of this size, it is noteworthy that none of these five patients displayed electroencephalographic evidence of the cerebral dysrhythmia seen in epilepsy, and that normal records were obtained in four relatives of two of them. These findings,

along with the negative family histories of this group for convulsions, would indicate a lack of the transmissible factor which predisposes to epilepsy. This would suggest that a local factor in the absence of an hereditary tendency may be insufficient of itself to produce seizures. In line with the fact that statistical studies of Lemmon, Gibbs, and Gibbs¹⁹ have demonstrated that 10 per cent of the normal population exhibit cerebral dysrhythmia, it is of interest to note that of a group of 305 patients with delirium tremens Rosenbaum, Lewis, Piker, and Goldman²⁰ found an incidence of convulsions in 9 per cent. The close approximation of these two figures suggests that possibly the patients who experienced convulsions were those who were endowed with a predisposition to epilepsy and were thus unable to withstand an additional insult, in this case the cerebral effects of alcohol.

Just how the changes of Paget's disease can act as a precipitating cause in lowering the convulsive threshold of patients predisposed to epilepsy cannot be stated with certainty. Several possibilities suggest themselves. The most obvious of these would seem to be compression of the cortex by the thickened calvarium. The anatomical studies of Leri,²¹ Marie and Leri,²² Knaggs,²³ and Wyllie¹² all show that, although there is a decrease in the vertical diameter of the intracranial cavity, its actual capacity remains undiminished due to the compensatory increase of the antero-posterior and transverse diameters. However, in some cases of osteitis deformans which came to necropsy (Marie and Leri²²) osseous protuberances from the inner table of the skull were observed. It is possible that in predisposed cases similar bony overgrowths might act as an epileptogenic agent by local compression of the cortex.

The association of generalized arteriosclerosis with osteitis deformans has often been commented upon and has been variously considered to be either the cause of the bone changes (Leri²⁴) or an accompanying manifestation of the same underlying toxic or metabolic disorder (Knaggs²³). Since convulsions are known to occur in some cases of cerebral arteriosclerosis, one might attribute their occurrence in Paget's disease to the vascular changes. The comparative rarity of seizures in this disease would again demand an explanation as to why they occur in some and are absent in the majority of cases. One cannot exclude the possibility that in predisposed cases cerebrovascular changes may be of sufficient severity to act as the precipitating agent. This may be equally true in cases of cerebral arteriosclerosis uncomplicated by Paget's disease.

If, on the other hand, Paget's disease is fundamentally a metabolic disorder (Gutman and Kasabach¹⁸), local changes in cerebral intra-cellular chemical processes (Putnam²⁵) secondary to the disturbed metabolism could account for the lowered convulsive threshold and in constitutionally predisposed individuals give rise to clinical epilepsy.

SUMMARY AND CONCLUSIONS

1 Two cases of Paget's disease (osteitis deformans) with convulsions are presented

2 Electroencephalographic findings in these patients, their available near relatives, and in five other cases of Paget's disease without convulsions are reviewed

3 The question of a constitutional predisposition to epilepsy is discussed in the light of these electroencephalographic findings

4 Evidence is offered to emphasize the relative rôles of hereditary and precipitating factors in the production of convulsive states

The authors wish to express their thanks to Dr Herta Seidemann for aid in interpretation of electroencephalographic records and to Mrs Ruth Simon for her technical assistance

REFERENCES

- 1 STRAUSS, H, RAHM, W E, and BARRERA, S E Electro-encephalographic studies in relatives of epileptics, *Proc Soc Exper Biol and Med*, 1939, xlii, 207
- 2 LOWENBACH, H Electro-encephalogram in healthy relatives of epileptics constitutional elements in "idiopathic epilepsy," *Bull Johns Hopkins Hosp*, 1939, lxxv, 125
- 3 LENNOX, W G, GIBBS, E L, and GIBBS, F A Inheritance of cerebral dysrhythmia and epilepsy, *Arch Neurol and Psychiat*, 1940, xlv, 1155
- 4 GIBBS, F A, and GIBBS, E L Atlas of electroencephalography, 1941
- 5 BRILL, N Q, and SEIDEMANN, H Electroencephalographic changes during hyperventilation in epileptic and non-epileptic disorders, *ANN INT MED*, 1942, xvi, 451-461
- 6 PAGET, SIR J Osteitis deformans, *Lancet*, 1876, vii, 14
- 7 MARIE, A Presentation de pieces et d'un malade aliene atteint de maladie de Paget, *Encephale*, 1927, xxii, 475
- 8 CAHANE, M, and CAHANE, T Paget's disease associated with epilepsy, *Riforma Med*, 1938, liv, 1604
- 9 KAY, H D, SIMPSON, S LEVY, and RIDDOCH, G Osteitis deformans, *Arch Neurol and Psychiat*, 1934, liii, 208
- 10 KASABACH, H, and GUTMAN, A B Osteoporosis circumscripta of the skull and Paget's disease, *Am Jr Roent*, 1937, xxxvii, 577
- 11 GRUNTHAL, E Cerebral findings in Paget's disease of the cranium, *Ztschr f d ges Neurol u Psychiat*, 1928, cxv, 35
- 12 NONNE, M Die Osteitis fibrosa in ihren neurologischen Beziehungen, *Deutsch Ztschr f Nervenheilk*, 1928, cv, 35
- 13 WILLIE, W G The occurrence in osteitis deformans of lesions of the central nervous system with a report of four cases, *Brain*, 1923, xlv, 336
- 14 GREGG, D Neurologic symptoms in osteitis deformans (Paget's disease), *Arch Neurol and Psychiat*, 1926, xv, 613
- 15 SCHWARZ, G A, and REBACK, S Compression of spinal cord in Paget's disease of vertebrae, *Am Jr Roentgenol*, 1939, xlii, 345
- 16 MOYLAN, R S Osteitis deformans with psychosis report of a case, *Ohio State Med Jr*, 1928, xxix, 70
- 17 KAUFMAN, M RAIPH Psychosis in Paget's disease (osteitis deformans), *Arch Neurol and Psychiat*, 1929, xxi, 828
- 18 GUTMAN, A B, and KASABACH, H Paget's disease (osteitis deformans), *Am Jr Med Sci*, 1936, cxci, 361

- 19 SUGARMAN, E. D. Osteitis deformans (Paget's disease of bone), *Am Jr Surg*, 1940, *xviii*, 414
- 20 ROSENBAUM, M., LEWIS, M., PIKE, P., and GOLDMAN, D. Convulsive seizures in delirium tremens, *Arch Neurol and Psychiat*, 1941, *xlv*, 486
- 21 LERI, A. Étude de la base du crâne dans la maladie de Paget, *Nouv Icon de la Salpet*, 1933, *xxvi*, 452
- 22 MARIE, P. and LERI, A. La crâne dans la maladie osseuse de Paget, *Bull et mem Soc. med d hôp d Paris*, 1919, *xliii*, 909
- 23 KNAGGS, R. L. Osteitis deformans (Paget's disease) relation to osteitis fibrosa and osteomalacia, *Brit Jr Surg*, 1925 *xiii*, 206
- 24 LERI, A. Études sur les affections des os et des articulations, 1926, Masson et Cie, Paris, p. 262
- 25 PUTNAM, T. I., and MEHRT, H. H. Chemistry of anticonvulsant drugs, *Arch Neurol and Psychiat*, 1941, *xlv*, 505

A THEORY EXPLAINING THE LOCAL MECHANISM FOR GASTRIC MOTOR AND SECRETORY CONTROL AND THE ALTERATION OF THESE FUNCTIONS IN UNCOMPLICATED DUO- DENAL ULCER *

By HARRY SHAY, M D , J GERSHON-COHEN, M D , D Sc (MED), and
SAMUEL S FELS, LL D , *Philadelphia, Pennsylvania*

THE symptomatology of duodenal ulcer is due in large part to the disordered gastric physiology. It is also true that if an adequate explanation for the disordered physiology were available, therapy could possibly be directed into more physiological channels than is now the practice. The disordered gastric function in duodenal ulcer, as is well known, takes the form of both motor and secretory changes. In uncomplicated cases, the abnormal motor phenomena are hyperperistalsis, hypertonicity, and hypermotility. The secretory abnormality is hypersecretion. These abnormal gastric findings have long been recognized, but no suitable explanation for their existence has as yet been given.

The presence of hydrochloric acid in the duodenum, in man, affects the gastric motor function¹. Especially striking are the effects produced by the addition of acid to the test meal in the achlorhydric subject. A water-barium meal, observed fluoroscopically in uncomplicated cases of gastric anacidity, shows a rapid gastric emptying, frequently in the absence of all peristalsis, and poor gastric tone. If for the water a hydrochloric acid solution of as little as 0.1 per cent concentration is substituted, gastric emptying is materially slowed, and instead, the almost continuous stream through the pylorus of the water-barium meal is replaced by an intermittency of gastric emptying resembling that in the normal individual¹. The addition of acid to the water-barium meal produces gastric motor delay also in the normal acid stomach, but with the weak acid mixtures the change is less marked than in the anacid individual and becomes more marked only with stronger acid solutions¹. When the weak hydrochloric acid solutions (less than 0.2 per cent) are slowly dripped into the duodenum a delay in gastric emptying is produced in all cases, although its intensity is influenced somewhat by the individual gastric acid response. These differences have already been fully discussed¹. With more concentrated solutions (greater than 0.25 per cent), this difference in behavior disappears and the delay in gastric emptying in all groups is very

* Read before The Section on General Medicine of the College of Physicians of Philadelphia, May 26, 1941.

Received for publication September 24, 1941.

From the Medical Research Laboratory Samuel S Fels Fund and the Gastro-Intestinal Division, Medical Service I, Mt Sinai Hospital, Philadelphia, Pa.

With the technical assistance of Herman Siplet, A B.

marked. The effects of such duodenal instillations have led us to believe that the *local* mechanism concerned in gastric emptying is controlled from the proximal duodenum and that the gastric hydrochloric acid is the intrinsic agent which when it arrives in the duodenum activates this mechanism. Furthermore, we have seen this mechanism operate in the human subject by prolonging pyloric closure. The intermittent emptying of the normal stomach may be visualized as follows. When gastric acid reaches the duodenum in concentration sufficient to activate the local mechanism, pyloric closure occurs until the neutralizing agents in the duodenum have reduced the acidity to a level which permits the pylorus to reopen. The stronger the acid concentration reaching the duodenum, the longer the periods of pyloric closure and the greater the prolongation of gastric emptying.

Free Acid Curves

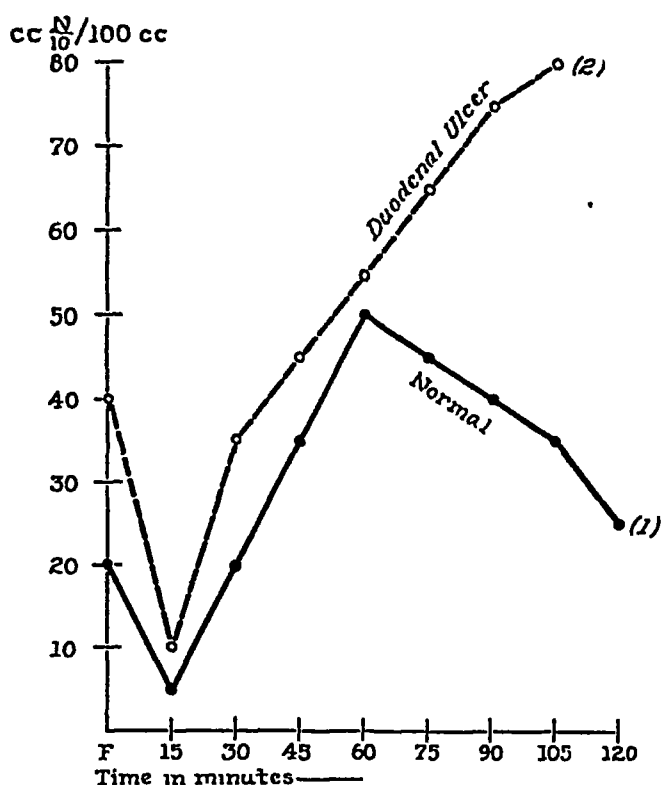


FIG 1

Figure 1, curve 1 represents the free acid curve usually obtained in the normal individual from the type of test meal we employed. Gastric emptying of a water-barium meal, if observed at short intervals, will be seen to follow closely in an inverse manner the pattern of this curve. This fluoroscopic observation will show that gastric evacuation is relatively active in the first 15 to 30 minutes after the ingestion of the water-barium meal. This corresponds to the period of gastric acid dilution by the meal. Gastric evacuation then slows materially—this corresponds to the period of increased

gastric acidity (Ascending limb of the curve) Evacuation is then again accelerated to correspond to the descending limb of the gastric acid curve (Water is quite capable of stimulating gastric secretion—Ivy)

In addition to the influence upon pyloric action, we have seen, too, striking effects of the acid upon gastric peristalsis and gastric tonus. Pyloric closure, caused by acid in the duodenum, is rapidly followed by a diminution of gastric peristalsis, which shows renewed activity as the acidity in the duodenum is reduced. Although a similar relationship between pyloric tonus and gastric tonus is more difficult to demonstrate in the human stomach, by our method of experimentation, we believe such a relationship exists.

In brief, then, gastric hydrochloric acid reaching the normal duodenum in concentration capable of stimulating the duodenal mechanism causes pyloric closure and decreases gastric peristalsis and tonus.

Duodenal ulcer is usually situated in the most active area of the above described mechanism, i.e., the cap. This location of ulcer coupled with the associated duodenitis of the adjacent duodenum results in partial destruction of the mechanism or a rise in the threshold of response. The normal intrinsic brake upon gastric emptying is reduced and the natural result is rapid gastric emptying with increased gastric peristalsis and tonus, three motor phenomena well known in uncomplicated duodenal ulcer.

We have demonstrated² that the duodenal instillation in man of many substances capable of stimulating the duodenal mucosa chemically or physically will activate a mechanism that depresses gastric secretion. From results obtained with weak solutions of hydrochloric acid we are convinced that this mechanism can explain the drop in acidity in the normal fractional gastric analysis after the peak of the gastric acid curve has been reached.³ In the disturbance of this mechanism in duodenal ulcer lies, we believe, the explanation for the secretory changes so frequently seen in this disease. Although we realize that no gastric secretory curve is pathognomonic of any disease, we believe that the hypersecretory extra-gastric curve occurs with such regularity in duodenal ulcer that it comes closest to representing a characteristic response (figure 1, curve 2).

Our previous studies³ indicate that the gastric hydrochloric acid acts as a self-regulator of its own secretion when it reaches the normal duodenum in proper concentration. To support this theory we believed it necessary to demonstrate that when hydrochloric acid of a concentration represented by the peak of the gastric acidity obtained in an individual for a particular gastric meal, entered the duodenum in small quantities, the normal gastric secretion would be depressed. Further, we believed that when acid representing the peak acidities reached in duodenal ulcer patients is instilled, it should fail to produce such depression in those cases which show an extra-gastric curve.

In order to test this view we selected normal and uncomplicated duodenal ulcer subjects. For each we determined the secretory response to a test meal

of 30 gm of zweibach and 300 cc of distilled water. In a few days this was repeated a second time with the standard meal in order to be certain that the test subject did not show any marked fluctuation in acid secretory response. The same length of tube for intubation for each patient was used throughout the series of tests in order to place the tip in as nearly the same area of the stomach as possible. Then with a similar test meal, with one Rehfuess tube in the stomach and another with its tip in the proximal duodenum, we introduced hydrochloric acid in proper concentration very slowly through the duodenal tube as the gastric meal was ingested. Gastric samples were removed at 15 minute intervals as in the standardization procedure and all specimens analyzed for free and total hydrochloric acid and total chlorides. The charts are characteristic of the results obtained.

Free Hydrochloric Acid Curves.

—Normal—

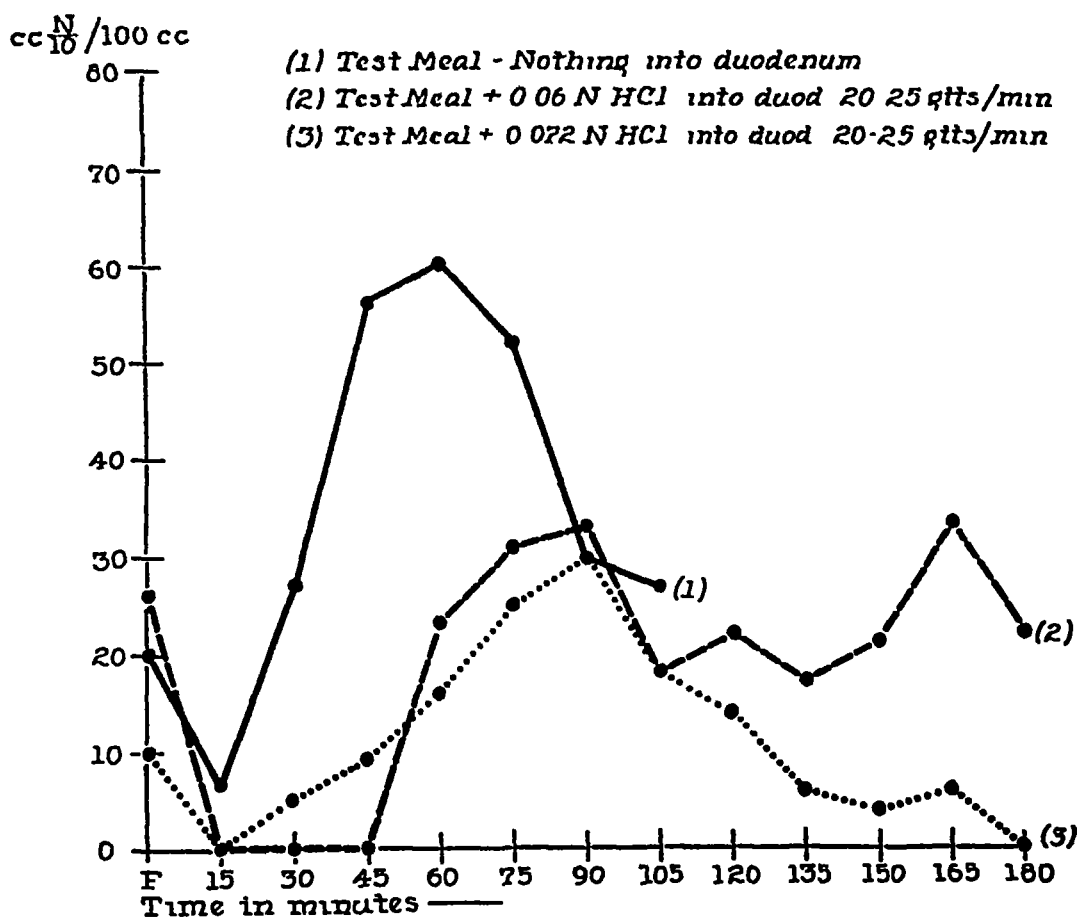


FIG 2

In figure 2, curve 1, one sees the response of a normal individual to our test meal. Figure 1, curve 2 shows the marked depression of acidity after a similar test meal when 0.06 N hydrochloric acid was dripped into the duo-

denum at the very slow rate of 20 to 25 drops per minute. When the concentration was increased to 0.072 N on another occasion, figure 2, curve 3, there was no striking change from curve 2. The concentrations of 0.06 N and 0.072 N were selected in this instance because they represented respectively the peak of free and total acidity obtained when the test meal alone was given. The total acid and chloride curves parallel the results recorded for the free acid.

Strikingly different are the results of similar experiments in uncomplicated cases of duodenal ulcer. Figure 3 illustrates the behavior of the free hydrochloric acid response in such a patient. Figure 3, curve 1 is the free hydrochloric acid response to the test meal. Figure 3, curve 2 represents the response to a similar meal when 0.079 N HCl was dripped into the duodenum at the rate of 20–25 drops per minute. The 0.079 N HCl in this instance represented the peak of the free hydrochloric acid seen in figure 3, curve 1. No change either in the peak or character of the free acid curve was produced. On other occasions, we increased the quantity of 0.079 N HCl instilled into the duodenum (figure 3, curve 3) and then the acid introduced into the duodenum was doubled in concentration (figure 3, curve 4). Even with this concentration there is no appreciable difference in the gastric acid curve produced when compared with figure 3, curve 1. Here, too, the total acid and chloride curves parallel the results shown for free acid.

In view of the results demonstrated¹ in our roentgen studies of the influence of hydrochloric acid in the duodenum upon gastric emptying, the difference in gastric motor effect of acid in the duodenum measured by fractional gastric analysis, seen in figures 2 and 3, is of particular interest. The retardation of gastric emptying in the normal individual (figure 2, curves 2 and 3) is very striking when compared with figure 2, curve 1, a change in gastric emptying from 105 minutes for curve 1 to 180 minutes for curves 2 and 3, or an increase in gastric emptying time of 71 per cent. The duodenal ulcer patient on the other hand (figure 3, curves 2 and 3) shows an increase of only 15 minutes in emptying time, a change which certainly must be considered within the limits of experimental error. Curve 4 showed a change of 30 minutes as compared with that obtained in curve 1, an increase of 25 per cent in gastric emptying time. These results corroborate those reported in our roentgen studies¹ and perhaps illustrate in a more quantitative fashion the effect of hydrochloric acid in certain concentrations in the normal duodenum upon gastric motor function and the lack of effect in the duodenal ulcer patient.

In previous studies we have shown² that the duodenal mechanism concerned with gastric motor function has a lower threshold of response than the one involved in gastric secretory control. Since we believe that in duodenal ulcer these duodenal mechanisms are depressed and not destroyed, it is of interest to note the more evident effect of the stronger acid solution (figure 3, curve 4) upon gastric emptying.

This duodenal mechanism, too, can explain the low and high gastric secretory normal responses. Although in all bodily functions we recognize an average normal response, we must also concede variants from this average which cannot be classed as pathological. In the same manner, we may

Free Hydrochloric Acid Curves

—Duodenal Ulcer—

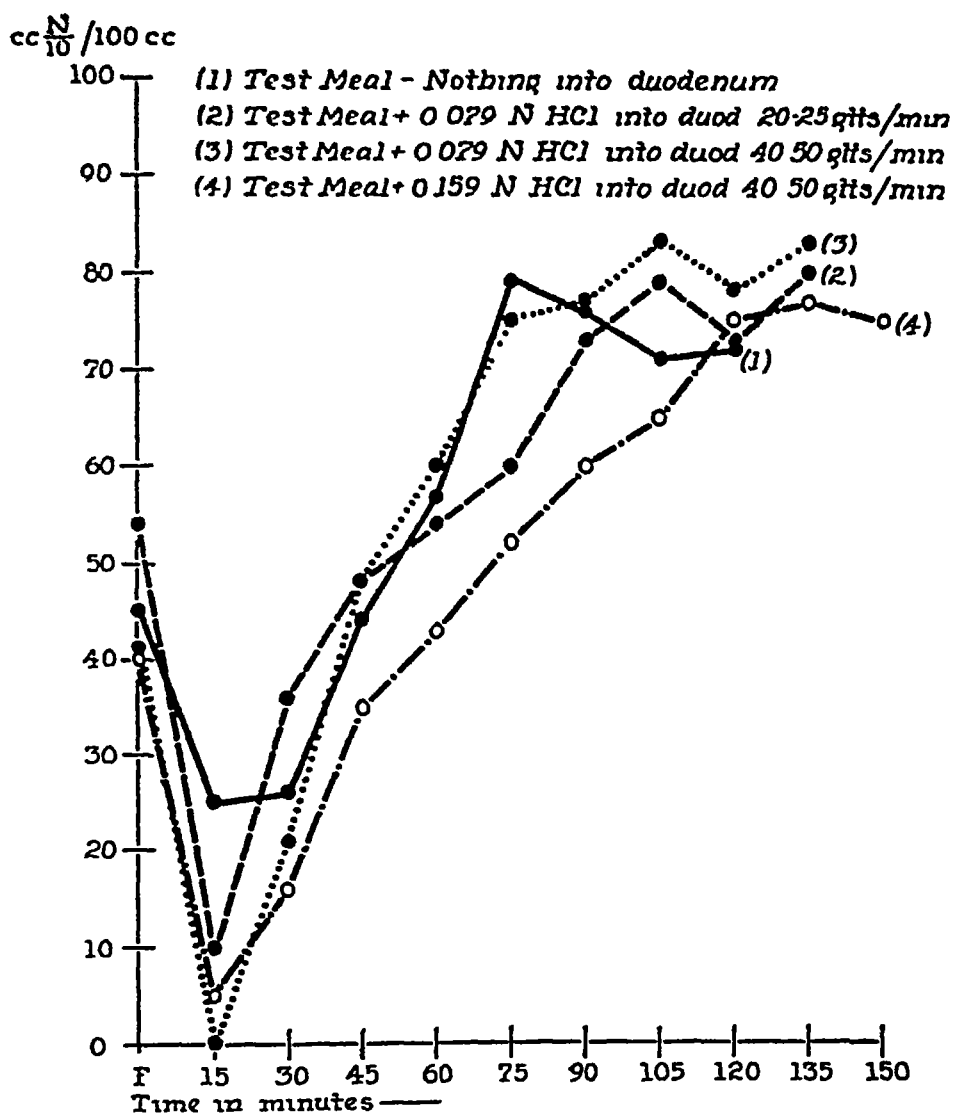


FIG 3

postulate variations from the average in the threshold of response. In an individual whose duodenal mechanism has a lower threshold of response, reaction to an acid concentration lower than average should result in a gastric secretory response that is lower. On the other hand, if the threshold of response is higher than average, gastric secretion will not be depressed

through duodenal stimulation until gastric acidity has reached a concentration capable of stimulating the mechanism and a patient with a high gastric secretory response will be found

This is illustrated in figure 4, a patient who, though normal from all examinations, showed a peak free acidity of 79 clinical units after our test meal, a response that is above the average normal. Yet the instillation of HCl of like concentration into the duodenum at the slow rate of 20–25 drops per minute produced a very sharp depression of gastric secretion after the ingestion of a similar meal

Free Acid Curves

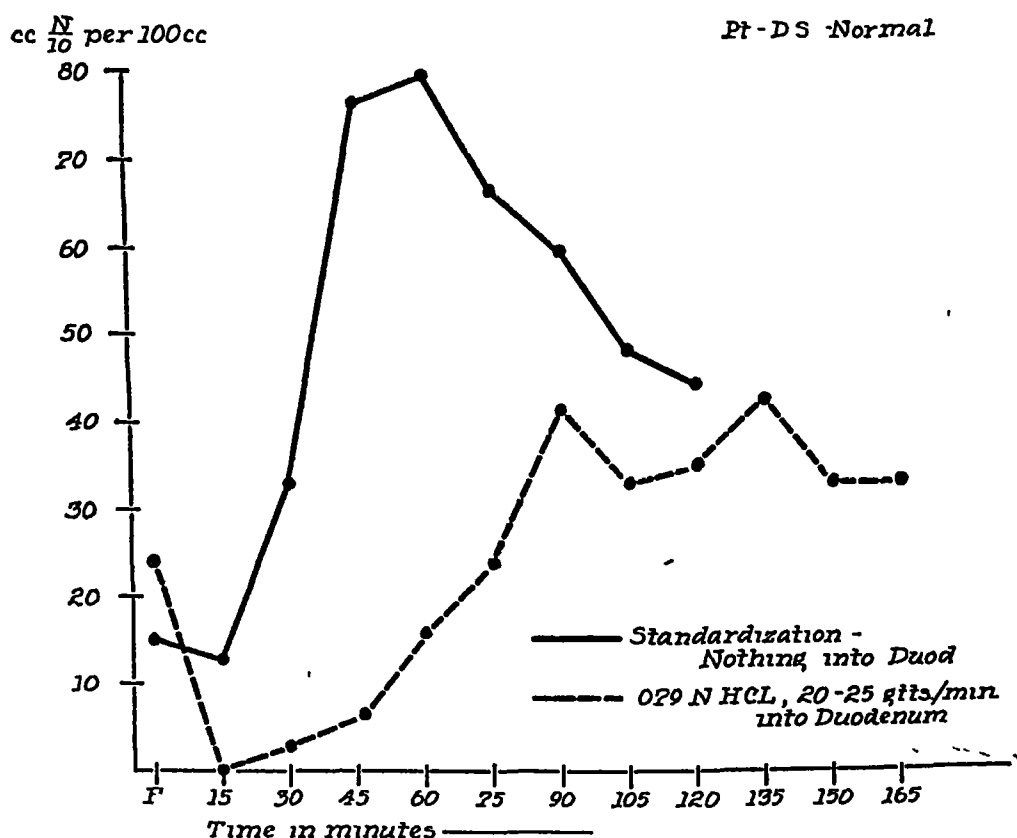


FIG 4

Summarizing, we believe that our studies for the first time present data which place in a single disturbed mechanism an adequate explanation for all of the abnormal gastric phenomena seen in uncomplicated duodenal ulcer. We believe that the normal duodenum houses a mechanism which is activated by gastric hydrochloric acid (intrinsic activator) when it reaches the duodenum in proper concentration. This mechanism is responsible for the *local factors* controlling both gastric emptying and gastric secretion. The gastric hydrochloric acid acts as a self-regulator of secretion. Further, we believe that the most active part of this regulating mechanism is located in the duo-

denal cap and proximal duodenum. When this mechanism is depressed by ulceration in the cap and inflammation of the adjacent duodenum, it fails to respond to the normal intrinsic activator when the gastric hydrochloric acid reaches it, resulting in (1) a failure to cause normal pyloric closure and decrease in gastric peristaltic activity and tonus, which result in rapid gastric

Patient HA (DU)

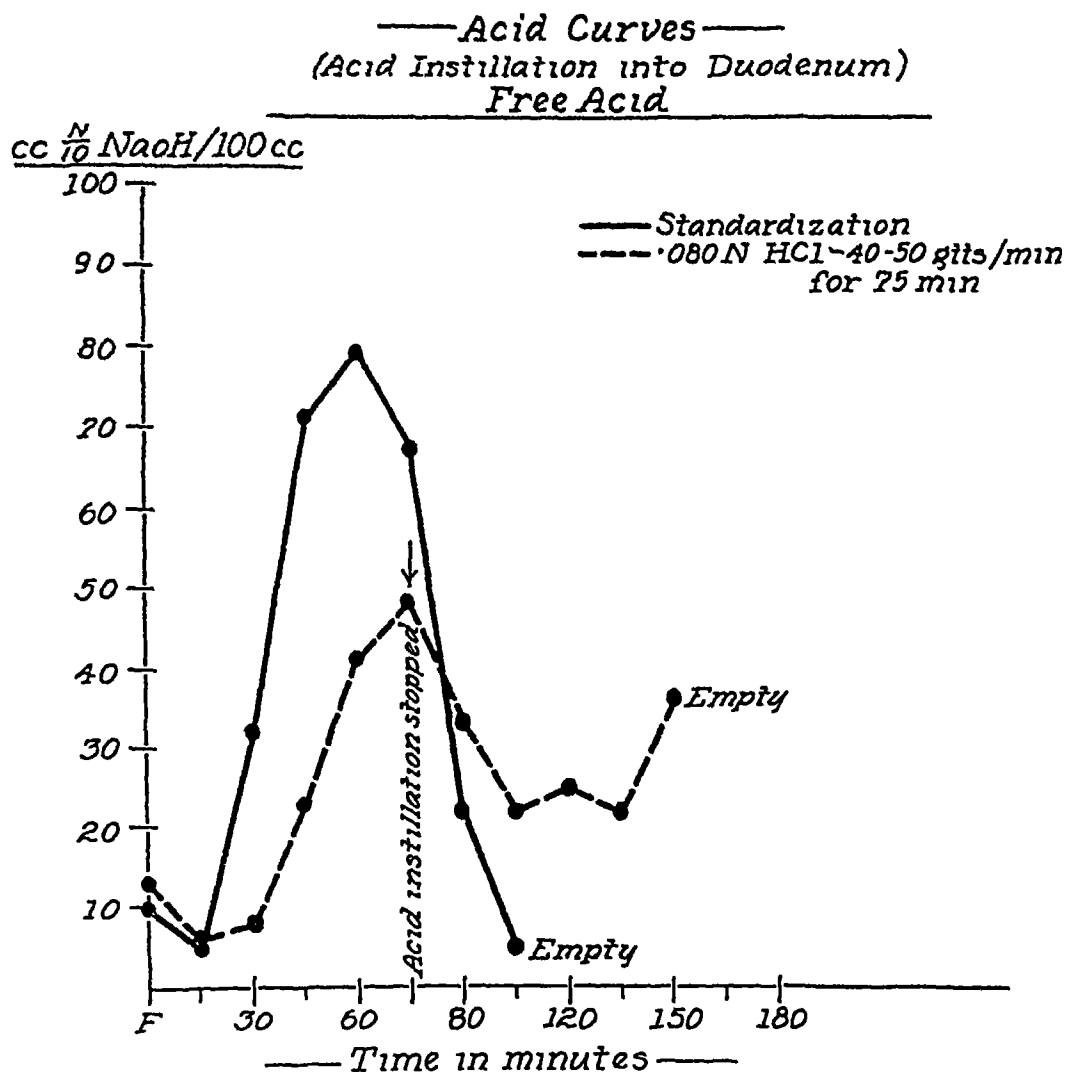


FIG 5

motility, hyperperistalsis, and hypertonicity, (2) a failure to put a check to active gastric secretion, with the resultant hypersecretory extra-gastric curve so frequently seen in duodenal ulcer.

In the difference in thresholds of response of the duodenal mechanisms concerned with gastric motor and secretory functions, may lie the explanation of the clinical observation advanced to discredit the rôle of gastric hyper-

secretion as a factor in the chronicity of duodenal ulcer. This observation holds that when duodenal ulcer patients are examined during the period of quiescence, or supposed healing, one frequently finds that although no abnormal gastric motor phenomena may be seen at such times, the gastric secretory response to a particular test meal does not differ in the slightest from the response observed at the time of clinical ulcer activity. We believe the explanation of this fact is as follows: the ulcer healed over, the associated duodenitis gone or diminished, duodenal function returns to a point at which the gastric acid reaching the duodenum is of sufficient concentration to activate the gastric motor mechanism, the one with the lower threshold of response, but not strong enough to activate the partially damaged gastric secretory mechanism, the one with the higher threshold of response.

Changes in the threshold of response of the duodenal mechanism concerned with gastric secretion may explain also the low and high acid gastric secretory responses seen in individuals otherwise normal. Because variations in response are physiological, such patients when tested respond in a normal manner. In duodenal ulcer the mechanism pathologically altered by the ulceration fails to respond to quite active stimulation. That the duodenal mechanism, even in ulcer, is not destroyed, but markedly depressed is shown by the fact that both the motor⁴ and secretory² duodenal mechanisms can be made to respond to extrinsic stimulants such as fats. Further, we have evidence that the duodenal mechanisms may, in some cases, when the ulcer activity subsides, recover sufficiently to yield a secretory curve that is normal in character although responding at a higher level—a picture similar to the normal high acid individual.

Patient H. A., figure 5, is the same one who gave the results illustrated in figure 3 except that the studies in figure 3 were done at a time when he was having ulcer symptoms. The studies in figure 5 were done five months later during which time he had been on an ulcer régime with resultant clinical quiescence of his ulcer. Figure 3 shows a failure of the duodenal secretory and motor mechanisms to respond to acid stimulation, figure 5 demonstrates a normal type of response in both mechanisms. We believe that the response in figure 5 represents a period of improved duodenal function and an increased sensitivity of the duodenal mechanisms possible during periods of ulcer healing and reduction of associated duodenitis.

We wish to stress again that the above expressed view is concerned only with the local mechanisms in the stomach and duodenum—that, however, we do not forget there is also a "remote control" mechanism for both gastric motor and secretory function, furthermore, that the local mechanism is not activated solely by the "intrinsic" hydrochloric acid but also responds to "extrinsic" agents introduced by food. These, through chemical or physical effects, upon reaching the duodenum may also bring the motor or secretory or both mechanisms into play.

BIBLIOGRAPHY

- 1 SHAW, H., and GERSHON-COHEN, J. Experimental studies in gastric physiology in man
II A study of pyloric control The rôle of acid and alkali, Surg., Gynec. and Obst., 1934, lvi, 935
- 2 SHAW, H., GERSHON-COHEN, J., and FINE, S. S. The rôle of the upper small intestine in the control of gastric secretion, the effect of neutral fat, fatty acid and soaps, the phase of gastric secretion influenced and the relative importance of the psychic and chemical phases, ANN. INT. MED., 1939, xiii, 294
- 3 SHAW, H., GERSHON-COHEN, J. and FINE, S. S. On a self-regulatory duodenal mechanism for gastric acid control and an explanation for the pathologic gastric physiology in duodenal ulcer, Am. Jr. Digest Dis. and Nutr. (to be published)
- 4 GERSHON-COHEN, J., and SHAW, H. Experimental studies on gastric physiology in man
III A study of pyloric control The rôle of milk and cream in the normal and in subjects with quiescent duodenal ulcer, Am. Jr. Roentgenol., 1937, xxxviii, 427-446

CASE REPORTS

THROMBOCYTOPENIC PURPURA AND CARCINOMA OF STOMACH, REPORT OF A CASE WITH PURPURA APPEARING AFTER SUBTOTAL GASTRECTOMY

By WILLARD H. WILLIS, M.D., *Utica, New York*

ISOLATED instances of thrombopenia and purpura associated with carcinoma of the stomach have previously been reported. These cases are of diagnostic interest because the clinical picture is frequently confusing. The initial complaint may be referable to the purpura, and the gastrointestinal symptoms, if present, may be ignored by the patient and the physician. The primary lesion may be small and difficult to diagnose by roentgen-ray as well as at the autopsy table. Even if carcinoma is suspected the characteristically extensive metastatic invasion of the bone marrow and lungs may not be discernible in roentgenograms.

In 1936 Jarcho¹¹ called attention to the fact that pathologically the cancers which are complicated by thrombopenia, the lymphangitic carcinomas of the lung,¹⁵ and the Krukenberg tumors of the ovary represent a "distinctive variety" of tumor metastasis for which he proposed the name "diffusely infiltrating" carcinoma. As the name implies, there is widespread microscopic invasion of various parts of the body. The lymphatics of the lungs and the ovary and the sinusoids of the bone marrow are common sites of metastasis. If the bone marrow is heavily involved, thrombocytopenia and myelophthisic anemia may occur. The stomach is by far the most common primary site of tumors capable of this type of metastasis.

Purpura and thrombopenia associated with carcinoma are quite unusual. It has even been suggested that the platelet count is usually increased in malignancy.¹⁴

Fifteen cases of carcinoma of the stomach associated with thrombocytopenic purpura have been found in the literature. Some outstanding clinical features of these are summarized in table 1. Although data now of interest to us frequently are omitted in these reports, there is enough information to suggest some clinical as well as pathological similarities. It will be seen that the patient is usually a young adult having varying degrees of anemia characterized by immature forms in the peripheral blood. Often the carcinoma was not discovered until autopsy. In three cases^{6, 10, 12} it was stated that it was difficult at autopsy to determine from the gross specimen if the lesion found in the stomach was malignant. Twice^{3, 4} the tumor was found at operation for splenectomy and exploration. In all except two cases (one⁶ in which only the tibia was examined and another⁸ in which no autopsy was done) there were striking metastases to bone which roentgen-ray at times failed to reveal. In no case was a sternal puncture done.

The lungs were not always described, but in four cases^{4, 9, 10, 11} there was microscopically widespread "lymphangitic" involvement. In one¹⁰ there was a typical Krukenberg tumor.

* Received for publication April 26, 1941.

TABLE I
Some Clinical Features of Cases Previously Reported

Author	Age	Sex	Outstanding Complaint	Initial Blood Count	Blood Smear	Metastases	Resection of Spleen
Schleip ¹	33	M	Hemoptysis, acute, abdominal pain	Plat "Diminished" R B C 2,911,000 Hgb 40% W B C 7,200	120 normoblasts and 15 megakaryoblasts per 100 W B C	Bone, lymph nodes, pleura	Not described
Dunnen ²	37	F	Bleeding tendency and gastro-intestinal	Plat 12,000 R B C 1,800,000 Hgb 50% W B C 3,500	Occasional normoblasts	Bone, liver, heart	Not described
Dunnen ³	29	F	Hemoptysis, gastro-intestinal	Plat 50,000 R B C 3,000,000 Hgb 45% W B C 7,400	Findings of secondary anemia only	Bone, liver	Not described
Seemann ⁴	38	F	Gastro-intestinal	Plat 150,000 R B C 4,200,000 Hgb 73% W B C 12,000	Many normoblasts and 2% leukoblasts late in course	Bone, lung, abdominal nodes, pancreas	Not described
Blum ⁵	46	M	Gastro-intestinal	Plat 16,000 R B C 4,000,000 Hgb 55% W B C 15,000	Normoblasts prominent, 4% myelocytes	Bone, lymph nodes, peritoneum, liver	Not described
Blum ⁵	58	M	Widespread pains	Plat 32,000 R B C 2,080,000 Hgb 35% W B C 4,600	5 normoblasts per 100 W B C, 45% of neutrophils segmented	Bone, liver, pleura, pancreas	Yes
Steinfeld ⁶	55	F	Gastro-intestinal	Plat 66,000 R B C 3,500,000 Hgb 60% W B C 7,200	Large numbers of normoblasts and immature granulocytes	None (tibia only bone examined)	Not described

TABLE I—(Continued)

Author	Age	Sex	Outstanding Complaint	Initial Blood Count	Blood Smear	Metastases	Roentgen-ray Evidence of Metastasis
Kohn ⁷	57	F	Debility, gastro-intestinal, purpura	Plat 10,000 R B C 1,600,000 Hgb 28% W B C 6,600	66% normoblasts, 3% myeloblasts	Bone, lymph nodes, peritoneum	Not described
Stallman ⁸	35	M	Gastro-intestinal	Plat 21,000 Hgb 65% W B C 12,500	Not described	Abdominal lymph nodes (at operation, no autopsy)	Not described
Lawrence ⁹	13	M	Gastro-intestinal	Plat "markedly diminished" R B C 3,000,000 Hgb 57% W B C 10,000	4 nucleated R B C per 100 W B C, many immature myeloid cells	Bone, lungs, mesenteric glands, adrenals, liver	Roentgen-rays of dorso-lumbar spine negative
Stebbins ¹⁰	21	F	Pain in legs	Plat 30,000 R B C 2,630,000 Hgb 50% W B C 11,600	No abnormal cells	Bones, lungs, spleen, ovaries, lymph nodes	Roentgen-rays of pelvis negative
Jarcho ¹¹	23	M	Purpura and back pain	Plat 18,000 R B C 3,040,000 Hgb 58% W B C 4,500	Nothing unusual described	Bone, lungs, liver, lymph nodes	Roentgen-rays of chest, femurs and vertebrae negative
McLeod ¹²	32	M	Purpura and acute abdominal pain	Plat 15,420 R B C 2,570,000 Hgb 58% W B C 17,400	5 normoblasts per 100 W B C	Bone, liver, lymph nodes, adrenal	Not described
Hompson ¹³	15	M	Weight loss, epigastric pain	Plat 46,000 R B C 2,100,000 Hgb 44% W B C 9,000	1 normoblast per 100 W B C, myelocytes present	Bone, lungs, liver	No definite evidence at first, later bone invasion demonstrated
Hompson ¹³	32	M	Weakness, bleeding tendency	Plat 30,000 R B C 2,600,000 Hgb 48% W B C 20,000	Numerous nucleated R B C, 12% myelocytes	Extensive widespread	Not described

The following case was observed at the Henry Ford Hospital. It is interesting because it is typical of this group in many respects and because purpura, appearing many months after subtotal gastrectomy, was the first clinical manifestation to suggest metastasis.

CASE REPORT

A S., a 42-year-old woman, first entered the hospital in August 1938, complaining of postprandial upper abdominal distress. Positive findings were roentgen-ray evidence of a persistent filling defect in the pyloric antrum, gastric hypoaclidity and occult blood in the stools.

A subtotal gastrectomy was performed by Dr. Roy D. McClure, August 21, 1938. An area of about 5 cm. in diameter in the antrum was polypoid and firmer than the adjacent tissue. In this area the mucosa was for the most part replaced by typical glands, columns and masses of neoplastic cells (figure 1). Throughout the remainder

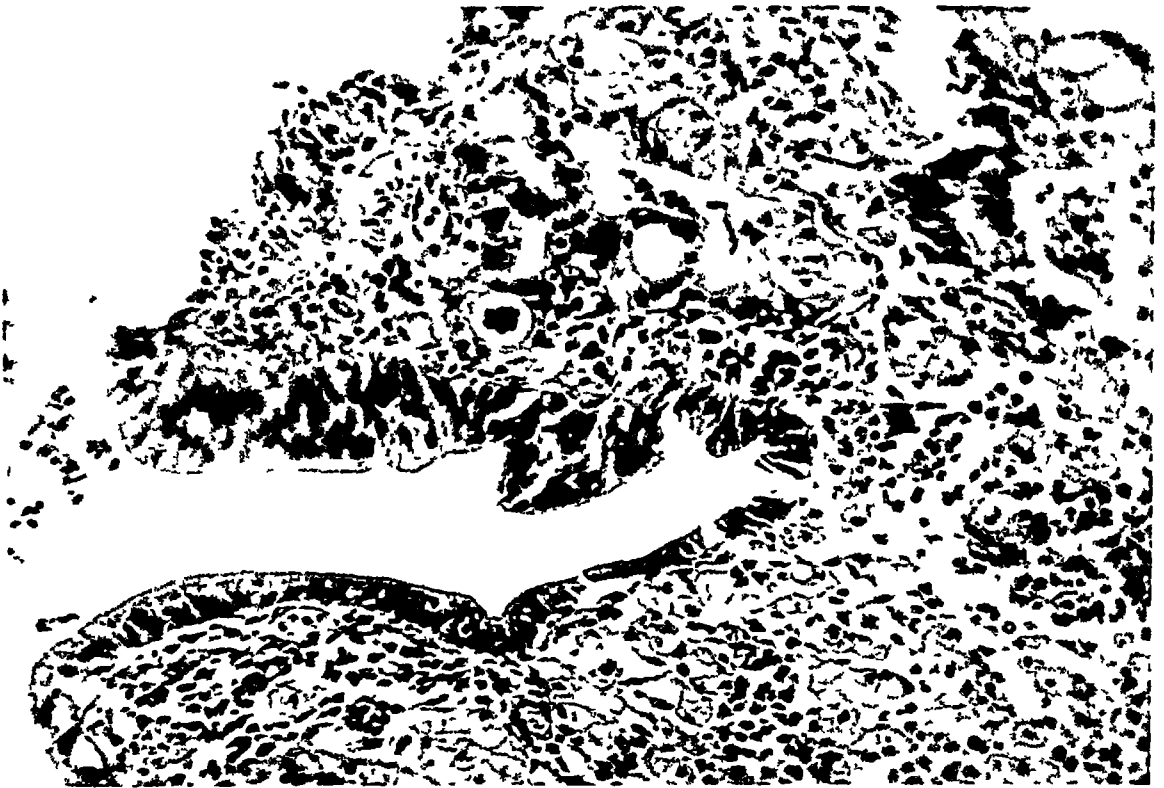


FIG 1 The margin of the malignant pyloric ulcer which was resected a year prior to the patient's death

of the wall, however, compressed alveoli or single cells invaded the stroma almost like inflammatory cells. A mesenteric lymph node contained malignant cells.

The patient remained well until the following May when she began to have pain in the lower extremities associated with purpuric lesions. In June 1939, she was admitted to the hospital again where she remained until her death late in August, just a year following the gastric resection. The blood count upon admission was erythrocytes 3,500,000, hemoglobin 10.5 gm., leukocytes 8,000, and platelets 50,000. An occasional normoblast appeared in the peripheral blood. Menorrhagia became an alarming symptom. Frequent blood transfusions and other forms of symptomatic treatment failed to bring about improvement.

Ten weeks prior to death, roentgen-rays of the lumbo-sacral spine failed to show evidence of metastasis. Roentgen-rays of the chest and long bones, three and two weeks prior to death respectively, were negative.

An autopsy was done by Dr. Frank W. Hartman. The only gross metastases were in the abdominal lymph nodes. Microscopically, however, there was involvement of the lungs, the bone marrow, an adrenal and the liver. The bone marrow of the sternum and lumbar vertebrae was extensively invaded by strands and masses of cells resembling the structure of the original tumor (figure 2). The tumor cells were sup-

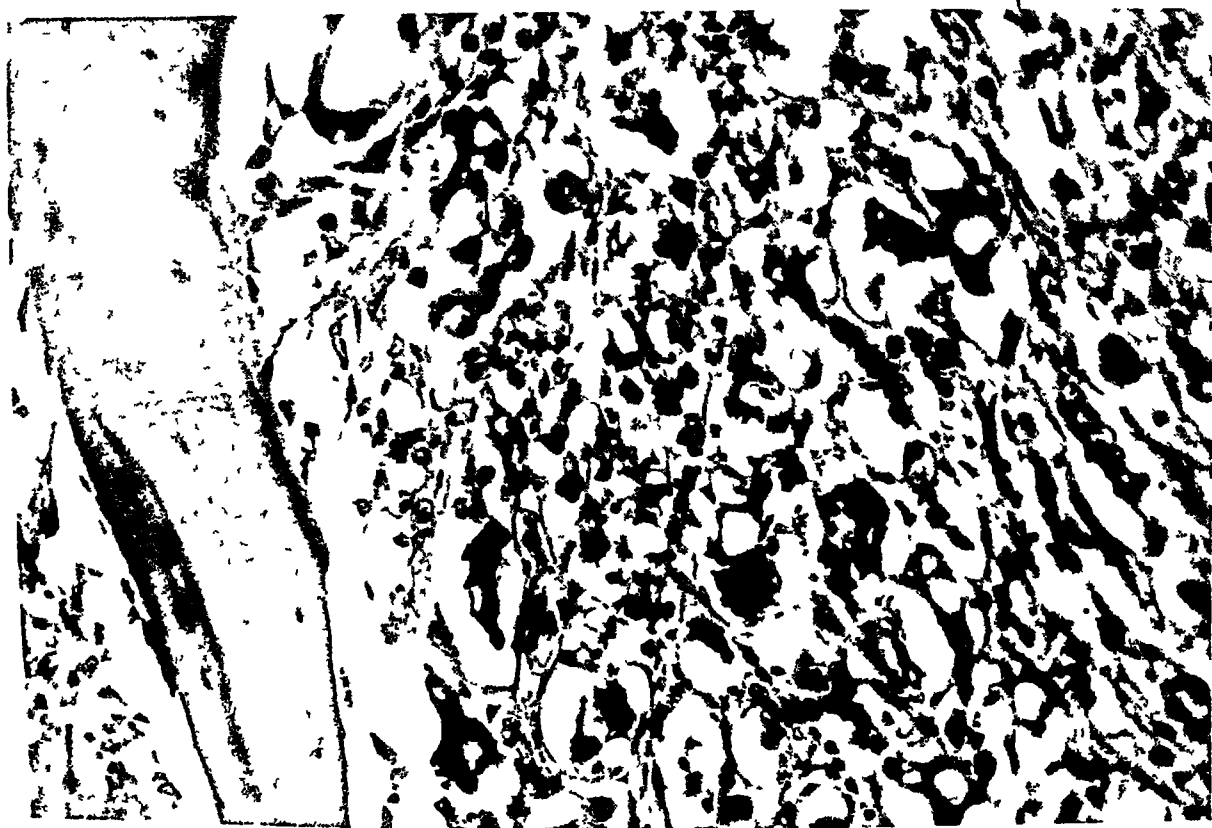


FIG 2 Showing diffuse infiltration of bone marrow by tumor cells

ported by a fibrous stroma almost completely devoid of normal marrow cells. Tumor was not present in some sections taken from the lumbar vertebrae. Here the marrow spaces contained a loosely arranged fibrous stroma, few normal cells were seen. The findings in the lungs were also striking. In many sections the lymph spaces were filled with malignant cells but nowhere was there alveolar destruction. The ovaries were not invaded.

SUMMARY AND DISCUSSION

A case of thrombocytopenic purpura secondary to replacement of bone marrow by a diffusely infiltrating carcinoma having its origin in the stomach is reported. It is distinctive because the purpura was the first symptom to suggest metastasis.

Thrombopenic purpura of obscure etiology should lead one to suspect the presence of a diffusely infiltrating carcinoma which commonly has its origin in the stomach. Likewise, in a person known to have or have had carcinoma of the stomach the appearance of purpura should suggest the possibility that this type of spread has occurred.

Röntgen-ray is not a reliable means of demonstrating the metastases either in the lungs or in the bone marrow. Studies of sternal marrow, however, should be of diagnostic value.

BIBLIOGRAPHY

- 1 SCHLIP, K. Zur Diagnose von Knochenmarkstumoren aus dem Blutbefunde, *Ztschr f klin Med*, 1906, lvi, 261-282
- 2 DÜNNER, L. Perniziose Anämie und Karzinom, *Berl klin Wchnschr*, 1921, lvm, 386-388
- 3 DÜNNER, L. Zur Ätiologie der Thrombopenie, *Berl klin Wchnschr*, 1921, lviii, 1107
- 4 SEEMANN, G., and KRASNOPOLSKI, A. Akut "Leukanämie" mit starker extramedullärer Blutbildung als Folge ausgedehnter Knochenmarksverdrängung durch Magenkrebsmetastasen (Zugleich ein Beitrag zur Kenntnis der diffus infiltrierenden Carcinome), *Virchow's Arch f path Anat.*, 1926, cclxii, 697-711
- 5 BLUM, K. Über symptomatische Thrombopenie bei Magencarcinom (Ein Beitrag zur Pathogenese der hämorrhagischen Diathesen), *Med Klin*, 1928, xxiv, 1200-1202
- 6 STEINFELD, E., and SHAY, H. Gastric carcinoma complicated by thrombocytopenic purpura, *Med Clin North Am*, 1930, viii, 923-929
- 7 KOHN, E. Symptomatische Thrombopenie bei malignen Tumoren des Knochenmarkes, *Med Klin*, 1931, xxvii, 767-768
- 8 STEINMAN, R. G. Coincidence of malignant tumor and purpura hemorrhagica, *Med Clin North Am*, 1931, vi, 1533-1538
- 9 LAWRENCE, J. S., and MAHONEY, E. B. Thrombopenic purpura associated with carcinoma of stomach with extensive metastasis, *Am Jr Path*, 1934, x, 383-390
- 10 STEBBINS, G. G., and CARNS, M. L. Thrombocytopenic purpura associated with adenocarcinoma of stomach in young adult, *Arch Path*, 1935, vi, 247-252
- 11 JARCHO, S. Diffusely infiltrative carcinoma, hitherto undescribed correlation of several varieties of tumor metastasis, *Arch Path*, 1936, viii, 674-696
- 12 MCFARLAND, C. E., and GOODALE, R. H. Adenocarcinoma of stomach with hemorrhagic diathesis, *New York State Jr Med*, 1938, xxxviii, 1339-1341
- 13 THOMPSON, W. P., and ILIUS, C. A. Clinical and hematologic picture resulting from bone marrow replacement, *Med Clin North Am*, 1940, xxiv, 841-853
- 14 NAFZGLI, O. Blutkrankheiten und Blutdiagnostik, 1931, Julius Springer, Berlin, p. 661
- 15 SCHATTFENBERG, H. J., and RYAN, J. F. Lymphangitic carcinomatosis of the lungs, case report with autopsy findings, *ANN INT MED*, 1941, vi, 1710-1721

THE WATERHOUSE-FRIDERICHSEN SYNDROME REPORT OF A CASE IN AN ADULT *

By A. T. KWEDAR, M.D., *Springfield, Illinois*

THE presence of purpuric or petechial spots on the skin, associated with a massive hemorrhagic destruction of both adrenals and the presence of a fulminating septicemia, is recognized as the Waterhouse-Friderichsen syndrome.¹

Seventy per cent of all cases reported are in children under the age of two years. This may be owing to the susceptibility and lack of immunity of children to the meningococcus. In Aegeiter's² review of the literature he found only six cases of Waterhouse-Friderichsen syndrome occurring in adults, only three of whom were over 50 years of age. Foucar,³ in 1936, reported one case in a 20 year old male and since that time all cases reported have been in children.

* Received for publication August 6, 1940

Including the case herein reported there are now about 77 cases of this syndrome in the literature. Kunstadter⁴ brought the literature to date in 1939, and there has been added one case by Levinson⁵ and two by McNamara and Connell⁶

CASE REPORT

A S, a housewife, aged 58 years, was first seen in her home at 2 p m on January 15, 1940. Her complaint was a mild upper respiratory infection of about 10 days' duration. She had been up and about doing her housework until the last two days, when she began to feel chilly and perspire freely. On the day of examination she felt a pain in her right ear and complained of nasal obstruction with a slight discharge.

Examination revealed a fairly obese white woman, not acutely ill. Temperature was 100.4° F, pulse rate 94 per minute, respirations 20 per minute, and blood pressure 150 mm Hg systolic and 84 mm diastolic. Head: There were two or three petechiae in the lower conjunctiva of each eye. The pupils were round and equal and reacted to light. The turbinates were swollen, the maxillary and frontal sinuses transilluminated light and were not tender. The left ear drum was normal, the right was not inflamed, but there was a hemorrhagic area in the posterior-superior part of the drum and the inner canal wall. The patient was edentulous. The tonsils were absent. Neck: The left tonsillar lymph node was slightly enlarged and tender. Chest: The lungs were clear to percussion and auscultation. The heart rhythm was regular, and the tones clear, no murmurs were heard. The heart borders were within normal limits. Abdomen: A healed surgical scar was present in the right upper quadrant (a cholecystotomy had been done on September 6, 1939). There were no palpable masses and no tender areas. A left inguinal hernia was present. Reflexes: There was no sign of meningeal irritation. The knee jerks were physiological and there was no Babinski.

Enteric-coated ammonium chloride, aspirin, a cough mixture, and a nasal spray of ephedrine sulfate were prescribed.

About 3 p m of the same day the patient began to vomit, this continued all afternoon. She began to have diffuse pain in the abdomen, for which she took an enema that gave no relief. At 7 p m the patient was sent a prescription containing morphine sulfate, bismuth subnitrate, and cerium oxalate in syrup of acacia to allay the vomiting. It stopped shortly after taking of the medicine.

The patient was seen for the second time at 10 p m of the same day. She now complained of a burning sensation in the thighs and back. She appeared very weak, pulse was soft and regular, 98 per minute, temperature was 101° F, respirations were 30 per minute. Numerous petechiae were present in the conjunctivae. The hemorrhagic area in the right auditory canal remained about the same. The skin of the chest had numerous petechiae, varying in size from pin-point to pin-head. The skin of the back presented a diffuse purplish hue and white dermatographism was marked. The abdomen was silent and there was no localized tenderness. The lungs were resonant but a few fine crepitant râles were present at the bases and expansion seemed to be somewhat restricted. The heart tones were very distant, the blood pressure was 78 mm Hg systolic, 50 mm diastolic. She was given 12 minims of adrenalin and taken by ambulance to St. John's Hospital.

Upon admission to the hospital she was given two ampules of coramine and one of caffeine sodio-benzoate. She was also given ¼ grain of morphine sulfate, for she was complaining bitterly of burning of the skin of the thighs and was crying for relief. A rigid examination revealed the corpus to be anterior and of normal size. A bedside film of the chest showed the lungs to be essentially negative except for a slight haziness at the base of both lung fields. Another ¼ grain of morphine sulfate was given for pain, and intravenous therapy was started with 1000 cc of 5 per cent

glucose in normal saline. Five grains of sodium phenobarbital were given directly into the tubing of the intravenous set for severe restlessness.

A blood count taken about midnight revealed Hemoglobin 14 gm per 100 c.c. red blood count 4 000 000; white blood count 17,000. Differential count showed polymorphonuclears 65 per cent, large lymphocytes 3 per cent, small lymphocytes 32 per cent. Slight anisocytosis and poikilocytosis of the red blood cells were present. Intra-cellular and extracellular diplococci were present in the blood smear (figure 1). A Gram stain of another smear showed this organism to be Gram negative. A blood culture later, indicated that the organism was a *Neisseria intracellularis* (meningococcus).

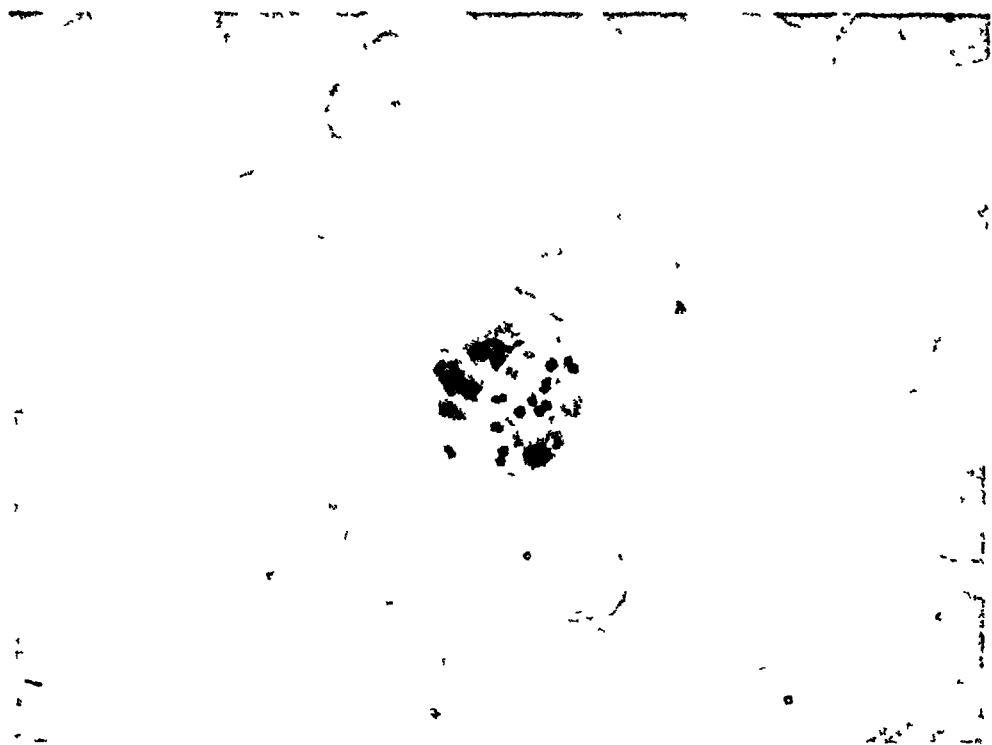


FIG. 1. Blood smear taken two hours before death, showing intra-cellular meningococci. Wright stain. 1035 X. (Photomicrograph by Dr. Aloysius Vass, Pathologist of Springfield Memorial Hospital.)

The patient was then given 20 c.c. of a 5 per cent solution of neoprontosil subcutaneously and 5 c.c. additional intravenously.

Her pulse was rapid and thready. Blotches appeared over the entire face, chest, abdomen and legs; here numerous petechiae and ecchymoses were present, some developing while the patient was being observed. The dependent skin assumed a peculiar blotchy lividity. The patient at 1:15 a.m. was still conscious, respirations were rapid, and she cried out incessantly that her skin was "on fire," especially that of the thighs and back. She was given $\frac{1}{2}$ grain of morphine sulfate and a final dose of five grains sodium phenobarbital intravenously. Restlessness was still present, even though she had received a total of one grain of morphine and 10 grains of sodium phenobarbital intravenously. At 1:30 a.m. she began to froth at the mouth and became comatose. She died at 2:10 a.m., January 16, 1940 (12 hours from the time she was first seen).

Autopsy (limited to an abdominal incision) * The body had already been completely embalmed. There was noted a very striking blotchy purplish mottling of the entire skin surface. There also appeared to be a considerable diffuse edema, especially of the face.

The most striking gross changes were noted in the adrenals. The right adrenal measured 6 by 3.2 by 1.2 cm, and weighed 9 gm. It was well preserved, in contrast to the left. The right adrenal was firm in consistency, but had a very dark red color throughout. It was surrounded by a large amount of rather adherent fat. On the cut surface, the cortex and medulla were readily distinguishable from each other and appeared to be of ordinary thickness. The dark red discoloration involved both medulla and cortex.

The left adrenal was considerably softened and had been torn to some extent by the embalmer's trocar. It was estimated that it must have had about the same dimensions and weight as the right adrenal. In the best preserved portions of the left adrenal the same very marked discoloration could be found as has already been described in the right.

Microscopic examination of both adrenals showed very extensive massive hemorrhage, with almost complete destruction of all of the tissue elements. The medulla, as far as could be determined, was completely destroyed. In the cortex at most places nothing could be found but large amounts of fresh blood, the original structure being represented only by remnants of connective tissue framework. In some places groups of cortical cells could still be discerned. The latter usually had opaque cytoplasm and possessed relatively large, rather faintly stained nuclei. Bacterial stains of these sections showed large numbers of Gram negative diplococci. Some of these apparently were free in the extravasated blood, whereas others were found within polymorphonuclear leukocytes. Similar organisms were seen within some of the swollen cells of the adrenal cortex. The adrenals were the only internal organs in which hemorrhages were noted.

Sections of the skin were taken through some of the discolored blotches noted grossly. There was present an intact epidermis of ordinary structure. Beneath it was a collagenous corium showing edema. All of the smaller blood vessels of the corium were considerably engorged, but no actual extravasation of blood could be demonstrated anywhere. Around a few of the engorged veins a little polymorphonuclear infiltration could be detected. Microorganisms could not be demonstrated in these sections.

The lungs showed pulmonary edema. There was an early acute myocarditis, as shown by the presence of a little diffuse polymorphonuclear infiltration of the myocardium. In the liver there was noted considerable fatty metamorphosis. The other organs showed nothing of particular interest.

COMMENT

The above case is reported because of the relatively infrequent occurrence of this syndrome in adults and also because of the paucity of reported antemortem bacteriological examinations. Although McLean and Caffey⁷ report the finding of positive blood smears taken from purpuric lesions of the skin in 83 per cent of cases of meningococcus meningitis, in the above patient the blood stream was overwhelmingly infected and ordinary smears taken from the finger contained numerous intracellular and extracellular meningococci. It was noted that considerable difficulty was encountered in obtaining blood from a stab wound of the finger, apparently owing to the marked hypotension.

* Performed by Dr. E. W. Light, Pathologist of St. John's Hospital.

The essential pathologic change noted was a complete destruction of the medulla of both adrenals, with only scattered remnants of cortical tissue framework remaining. Bacterial stains showed the meningococci present in the adrenals. Sections of the purpuric skin lesions showed only engorged blood vessels of the corium with no actual extravasation of blood.

Clinically the patient presented a picture, at the onset, of an ordinary upper respiratory infection. Chills and fever soon followed, with petechiae and purpuric lesions of the skin. Then there appeared vague abdominal pain and vomiting, soon after which the patient presented a picture of severe circulatory collapse. While crying out with burning pain in the skin, she died within 12 hours of the onset.

REFERENCES

1. SACHS, MITON S. Fulminating septicemia associated with purpura and bilateral adrenal hemorrhage—Waterhouse-Friderichsen syndrome: report of two cases with review of the literature, *ANN INT MED*, 1937, x, 1105-1114.
2. AIGERTER, E. E. The Waterhouse-Friderichsen syndrome. A review of the literature and a report of two cases, *Jr Am Med Assoc*, 1936, cxi, 1715-1719.
3. FOLCAR, F. H. Acute fulminating meningococcus infection with bilateral capillary hemorrhage of the adrenals as the most striking gross pathologic lesion, a case report, *ANN INT MED*, 1936, ix, 1736-1746.
4. KUNSTADTER, R. H. The Waterhouse-Friderichsen syndrome, *Arch Pediat*, 1939, lvi, 489-507.
5. LEVINSON, S. A. The Waterhouse-Friderichsen syndrome, *Jr Pediat*, 1939, xiv, 506-516.
6. MCNAMARA, F. P., and CONNELL, W. J. The Waterhouse-Friderichsen syndrome, *Jr Iowa State Med Soc*, 1938, xxviii, 197-199.
7. MCLEAN, S., and CAFFEY, J. Endemic purpuric meningococcus bacteremia in early life: diagnostic values of smears from purpuric lesions, *Am Jr Dis Child*, 1931, xlii, 1053-1074.

EDITORIAL

CRUSH SYNDROME

THE occurrence of fatal renal insufficiency following crush injuries of the limbs was first clearly described by Bywaters and Beall¹ in 1941, who reported four cases and described a typical clinical syndrome. Their observations have since been confirmed by a number of other British writers.

These cases were all victims of bombing disasters and had been buried several hours under the debris of wrecked houses in such a manner that the muscles of the limbs or trunk had been subjected to intense pressure. On release, in some cases there was evidence of severe local trauma, with weals like those following burns, abrasions, ecchymoses, and even incipient gangrene, with some local edema. More often evidence of local injury was slight, and there might be merely some local erythema, so that the serious nature of the injury is easily overlooked. According to Patey² the syndrome may follow simple compression without actual crushing of the muscle. A similar condition has been reported following motor accidents, after compound fractures of the leg, and after protracted, difficult labor.

Within a few hours the injured limb became markedly swollen. The tissues at the site of compression became intensely indurated, and softer edema extended over the entire limb and often onto the trunk. Probably as a result of the edema, the patient was unable to move the limb, there were paresthesias or anesthesia, and arterial pulsation was partly or completely obliterated.

When first released, patients might be in shock, but as a rule their condition was good. Shock developed some hours later, with a fall in blood pressure and acceleration of the pulse rate. This was accompanied by sweating and evidences of dehydration, a high hemoglobin content and some rise in plasma protein. Shock was combated successfully by means of injections of serum or plasma or by transfusions, and the patients were rarely in shock for more than a few hours. It did not appear to be a major factor in the production of the subsequent renal failure.

In spite of recovery from acute shock, oliguria appeared quickly and in the severe cases became extreme, even to the point of complete anuria. There was some general edema, thirst, often persistent vomiting, with anxiety or drowsiness. Death occurred in uremia, usually on the fifth to the eighth day.

The urine at first was often rusty in color, and it contained albumin, red blood cells and many pigmented casts. Later the albumin and the formed elements tended to disappear, but the urine was pale and the specific gravity

¹ Bywaters, F. G. L., and Beall, D. Crush injuries with impairment of renal function. *Proc. Med. Soc.* 1941, 1, 427.

² Report of the Royal Society of Medicine, Section of Surgery. Effects on the limbs of limb compression. *Brit. Med. J.*, 1941, II, 884.

and urea concentration were low. The concentrating power and the capacity to reabsorb chlorides were markedly impaired. It resembled a glomerular filtrate. The most striking changes reported in the blood were a progressive rise in blood urea to 140 mg per cent or higher and in the serum potassium to about 25 mg per cent. Patients who recovered showed, after about a week, a gradual fall in blood urea and an increase in the volume and specific gravity of the urine.

At necropsy the significant changes noted were largely limited to the muscles and to the kidneys. The muscles showed local necrosis of varying degree and often patchy hemorrhages. A striking feature was marked pallor of the injured muscle, like "fish flesh," resembling the changes seen in paralytic myoglobinuria of horses.³ There was marked edema, so that the muscle tissue was under great tension within the fascial compartments.

The kidneys were swollen and edematous. The glomeruli showed little or no change. The tubular epithelium showed degenerative changes which were especially marked in the ascending limb of the loop of Henle and in the distal convoluted portion. The cells showed basophilic cytoplasm, pyknosis of the nuclei, or actual necrosis. The lumina of many of the tubules were blocked by orange colored or dark brownish granular casts made up of or containing hemoglobin-like pigment. These casts were also found in some of the collecting tubules in the medulla. Dunn et al.⁴ have described (in two cases) peculiar lesions in the ascending limb of Henle's loop in the boundary zone between the cortex and medulla. These consisted of aneurysmal dilatations of the tubule, 40 to 80 micra in diameter, filled with albuminous material. These tended to rupture into the interstitial tissue or into an adjacent venule and extrude the albuminous contents. There was also evidence of regeneration and proliferation of epithelial cells. The lesions, in general, resembled those seen in some cases of experimental tubular nephritis. The location of these lesions has been attributed to a change to an acid reaction of the urine at this level.

The exact pathogenesis of the renal injury has not been definitely established. Shock undoubtedly may contribute to the early oliguria. Many of these cases, however, had not shown severe or prolonged shock. Furthermore lesions of this type were not seen in cases suffering from shock as a result of injuries of other types.

The lesions resembled those which followed transfusions of mismatched blood, and many of the cases had been transfused. However, they did not show the usual symptoms of transfusion reactions, and a number of them had received only plasma or serum, not whole blood. The blood plasma of the patient, in a few cases in which it was examined, was not high colored.

The syndrome is most easily explained on the hypothesis that the kidneys

³ GILMOUR, J. H. Myoglobinuria and crush syndrome (letter to editor), *Lancet*, 1941, 1, 524.

⁴ DUNN, J. S., GILLESPIE, M., and NIVEN, J. S. F. Renal lesions in two cases of crush syndrome, *Lancet*, 1941, 11, 549-552.

are injured by toxic substances liberated from the damaged muscle. It is not yet certain, however, just how this is brought about. The resemblance to myohemoglobinuria of horses is emphasized by the demonstration by Bywaters and Deloy⁵ that the pigment in the urine of two cases of crush syndrome gave the spectrum of oxymyohemoglobin. The spectrum of the carboxy- and meta-derivatives also corresponded to those of myohemoglobin.

The disease in horses occurs in animals which have been rested for a few days on a full carbohydrate-rich diet, shortly after they have been put back to heavy work. The animals become lame and may be unable to stand or walk. The muscles feel indurated and the urine is highly colored with myohemoglobin. Death often follows after a few days. The muscles are very pale, like fish flesh, and show degenerative changes and necrosis. Pigmented casts are found in the kidney tubules. Carlstrom reported finding an excess of glycogen in the muscles. The changes have been attributed to an excess production of lactic acid, together probably with some impediment to the local circulation. Gilmour believes that a similar mechanism is concerned in the development of the peculiar muscle lesions in crush syndrome.

A condition similar to the disease of horses has been reported as a great rarity in man. In one case quoted by Bywaters,⁵ exercise was followed by a rise in plasma potassium, such as occurs in cases of crush syndrome, suggesting an increased permeability of the muscle cells. Similar degenerative changes in the muscles with myoglobinuria have been reported from Konigsberg in human cases who had eaten fish poisoned by resinous acids, the by-products of cellulose factories.

Whether or not myohemoglobin is itself directly toxic has not been proved. Mere blockage of the tubules by casts does not seem an adequate explanation. There seems to be also a diffuse toxic injury to the tubular epithelium. In all probability the toxic substance arises in the injured muscles.

Thus far no type of treatment has been shown to be effective. The procedures used have been based, for the most part, on the theory that the disease is caused by toxic substances liberated from the muscles. Shock should be combated by the use of plasma or serum rather than whole blood. McMichael⁶ suggested applying a tourniquet proximal to the injury and packing the limb in ice immediately after release to retard the penetration of toxic substances into the circulation. Attempts have been made to secure diuresis by forcing fluids, by mouth if possible, and by vein as glucose or salt solution. In one case, however, extreme oliguria persisted, in spite of the administration of 25 liters of fluid during a period of several days. Among other procedures suggested have been the administration of alkalis, the use of suprarenal cortical extract on the assumption that the high blood potassium indicated a cortical insufficiency; decapsulation of the kidneys, which

⁵ BYWATERS, E. L. G. and DELOY, G. E. Myohemoglobinuria (letter to editor), *Lancet*, 1941, 1, 728.

has been followed by recovery in a few cases of anuria following mismatched transfusions; local decompression by incisions to release edema and lower tension, and amputation. In one case reported by Bywaters, however, amputation 36 hours after admission to the hospital did not alter the course of the disease, and the patient died in uremia several days later.

The mortality in outspoken cases was high. Bywaters stated that death occurred in two thirds of the cases who were observed in hospitals. There was no close relationship between survival and the duration of compression or the conspicuousness of the superficial evidences of trauma, although the extent of the injury is important. Recovery did occur in spite of marked oliguria and azotemia.

Improvement in treatment depends upon obtaining a precise knowledge of the pathogenesis of the renal injury. This can probably be secured only by the experimental production of the disease. The problem does not appear to be very difficult, and its solution should be of great practical value in the present emergency.

BOOK REVIEWS

Clinical Roentgenology of Pregnancy By WILLIAM SNOW, M D 178 pages, 26 × 17 cm Charles C Thomas, Springfield, Illinois 1942 Price, \$4.50

This book, according to the author, is an attempt to clarify and simplify the subject of roentgen pelvimetry and cephalometry. In this he succeeds very well, his explanation of the technic being clear and easily understood. The book is evidently written for the roentgenologist and obstetrician, more for the former, and should be a great help to one with a general knowledge of roentgen-ray technic who is just entering upon the comparatively new subject of pelvimetry, cephalometry and soft tissue diagnosis by the roentgen-ray.

The author emphasizes the safety of the roentgen-ray in pregnancy, in the dosage used for diagnosis. He apparently feels that there is no need for roentgen examination as a routine, but that it should be reserved for those cases in which an abnormality is suspected.

The Caldwell and Moloy classification of pelvis is followed, which appears to be the best we have to date and the most generally accepted.

The section on soft tissue diagnosis is very well done, and the author's claims in this field are quite modest.

The principal criticism concerns the section on the mechanism of labor, which differs somewhat from that generally taught and leaves something to be desired.

The entire book is profusely illustrated with clear and concise reproductions of films, and the last one third consists of case reports in which all of the films are reduced equally, the original being four and one half times the size of the reproduction. This is in order "that the reader may practice making the measurements."

L H D

Manual of Clinical Chemistry By MIRIAM REINER, M Sc 282 pages, 18 × 13 cm Interscience Publishers, Inc., New York 1941 Price, \$3.00

This pocket-sized manual of some 280 pages is quite comprehensive and covers the subject of clinical chemistry quite comprehensively. It is designed primarily to correlate routine analysis with clinical observation.

The first section is devoted to a discussion of the fundamental principles of quantitative analysis and the "rules of the game" so to speak. In successive chapters the author in concise yet complete fashion describes the principles, procedures, and reagents utilized for most of the methods used in a clinical laboratory. Each procedure is accompanied by a reference to the original work on the subject.

The reviewer found particularly interesting and helpful the sections on toxicological procedures and those describing the various functional tests. On the whole the methods are the classical procedures with such modifications as the author has found satisfactory.

The busy practitioner or technologist who is interested only in the methods of clinical chemistry should find this little volume invaluable.

E J P

The Autonomic Nervous System By JAMES WHITE, M D, and REGINALD SMITHWICK, M D 469 pages, 24 × 16 cm The Macmillan Company, New York 1941 Price \$6.75

The second edition of *The Autonomic Nervous System*, written by James C. White and Reginald Smithwick, will be a splendid contribution to the medical libraries of the

country. The authors have brought together in an impartial manner the available facts on this important subject and pictured them in simple language and illustrations. The anatomy and physiology as well as the clinical facts relating to the system, are so clearly portrayed that they can be readily understood by the advanced student in medicine or surgery. Although the advanced student in the neurological field may not agree with the authors in all details he will not find them far afield in the fundamentals. It is indeed fortunate, as well as timely, that this comprehensive edition should appear on a subject that is so little understood by the medical profession in general.

After a careful review of the book I heartily recommend it to the practitioners of all branches of the medical profession.

T B A

The Proceedings of the Charaka Club Volume X 260 pages, 23.5 × 15.5 cm Williams and Wilkins Company Baltimore 1941 Price, \$5.00

From one of the essays in this book by Dr. Bernard Sachs, entitled "Early Years of the Charaka Club," we learn that this organization is composed of physicians interested in the cultural aspects of medicine. There were five original members who effected the organization of the club in 1899. The present volume is the tenth of the "Proceedings" of the club. It is understood that the first two volumes are scarce.

This book is composed of 23 papers read before the club. The historical essays include papers on Barbara Fritchie, and Dr. William Tyler who was a member of the United States Sanitary Commission during the Civil War. Literary papers of medical interest are represented by such titles as "Fig Leaves for Shakespeare and Montaigne," "The Mystery of Robert Seymour" who illustrated Dickens' "Pickwick Papers," and "A Note on the Satirical Writings of Richard Grant White."

Papers on artistic subjects include "Ramblings of a Rug Addict," "The English Garden," and "Life and Death Masks." Medical history is well represented by the following papers: "Galen on Malingering, Centaurs, Diabetes and Other Subjects," "A Little Book on Children and How It Grew" (This describes "De Aegritudinibus Infantium" of Leonello Faventino de Victorius [Ingolstadt 1544]), and "The Medical Notions of a Roman Gentleman in the Second Century, A.D."

The book is attractively printed and is delightful to read.

J E S

COLLEGE NEWS NOTES

NEW LIFE MEMBER

Dr Maurice Lewison, F A C P, Chicago, Ill, became a Life Member of the American College of Physicians on March 17, 1942

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of Publications by Members are gratefully acknowledged

Books

- Dr Edward S King, F A C P, Winston-Salem, N C—"Bacteriology Laboratory Methods",
- Dr Francis P McNamara, F A C P, Dubuque, Iowa—"Collected Reprints and Bibliography of the Finley Hospital Medical Staff, 1927-41",
- Dr Cecil Striker, F A C P, Cincinnati, Ohio—"First Annual Proceedings of the American Diabetes Association",
- Dr Zolton T Wirtschafter (Associate), Cleveland, Ohio—"Diabetes Mellitus"

Reprints

- Dr Robert S Berghoff, F A C P, Chicago, Ill—1 reprint,
- Dr Edward G Billings, F A C P, Denver, Colo—1 reprint,
- Dr Allen H Bunce, F A C P, Atlanta, Ga—3 reprints,
- Dr Guy W Carlson, F A C P, Appleton, Wis—1 reprint,
- Joseph R Darnall, F A C P, Lieutenant Colonel, (MC), U S Army—1 reprint,
- A Allen Goldbloom, F A C P, Major, (MRC), U S Army—1 reprint,
- Dr Isidore W Held, F A C P, New York, N Y—2 reprints,
- Dr LeMoyné Copeland Kelly, F A C P, New York, N Y—3 reprints,
- Dr Donald S King, F A C P, Brookline, Mass—8 reprints,
- Dr Charles J Koerth (Associate), San Antonio, Tex—2 reprints,
- Dr Nils P Larsen, F A C P, Honolulu, T H—1 reprint,
- Dr William G Leaman, Jr, F A C P, Philadelphia, Pa—1 reprint,
- Dr Frederick W Mulsow, F A C P, Cedar Rapids, Iowa—2 reprints,
- Dr Louis Bonner Owens, F A C P, Cincinnati, Ohio—1 reprint,
- Dr Herbert J Schattenberg (Associate), New Orleans, La—27 reprints,
- Dr Harry W Shuman, F A C P, Rock Island, Ill—1 reprint,
- Dr Louis H Sigler, F A C P, Brooklyn, N Y—1 reprint,
- Dr Merritt Henry Stiles, F A C P, Philadelphia, Pa—6 reprints,
- Dr F Erwin Tracy, F A C P, Middletown, Conn—1 reprint

We also acknowledge receipt of thirty-seven reprints from Evans Memorial, Massachusetts Memorial Hospitals, Boston, many of which were written by members of the College

REGIONAL MEETING OF WESTERN PENNSYLVANIA MEMBERS

Under the Governorship of Dr R R Snowden, F A C P, Pittsburgh, the Fellows and Associates of the College in Western Pennsylvania held their annual regional

meeting, March 25, 1942. At the scientific session conducted during the afternoon there was a demonstration of the electron microscope. The demonstration consisted of informal discussions as to the physical principles and the mechanism of the instrument, and the technic of the preparation and magnification of the specimens. Each member was given an opportunity to view the actual image. After the demonstrations there were further discussions of the use of the electron microscope in the various fields of science, including medicine. Dr. William S. McEllroy, F.A.C.P., Dean of the University of Pittsburgh School of Medicine, presided, and Charles S. Smith, Jr., Ph.D., and Donald A. Wilson, Ph.D., both of the Department of Physics of the University, participated in the discussions.

The scientific session was followed by cocktails and dinner. After dinner the members were shown moving pictures of "Pearl Harbor," "The Normandie," and "Russia Stops Hitler."

MONTANA A. C. P. MEMBERS HOLD REGIONAL MEETING

The Montana branch of the American College of Physicians met in Missoula, February 21-22, 1942, this being the seventh annual meeting of this group.

Dr. Fred Schenck, F.A.C.P., of Great Falls, presented a paper on "The Treatment of Edema"; Dr. H. R. Cox, of the U. S. Public Health Service Laboratory, Hamilton, Mont., presented a paper with kodachrome illustrations on his work with "Encephalitis"; and Dr. M. V. Hargett, also of the U. S. Public Health Service Laboratory at Hamilton, presented a paper on "Yellow Fever."

On February 22 the members were the guests of Dr. R. R. Parker and staff at Hamilton, Mont., where the group was conducted through the U. S. Public Health Service Laboratory and where they saw vaccine produced for yellow fever, Rocky Mountain spotted fever, and typhus fever. This laboratory is the second largest public health laboratory in the world.

General arrangements for this regional meeting were made by Dr. Ernest D. Hitchcock, F.A.C.P., College Governor for Montana, Dr. Allen R. Foss, F.A.C.P., of Missoula, Secretary of the Montana group, Dr. Paul Ritchey, F.A.C.P., of Missoula, and Dr. Meredith Hesdorffer (Associate), of Missoula.

REGIONAL MEETING OF WESTERN NEW YORK MEMBERS

Under the Governorship of Dr. Nelson G. Russell, Sr., College Governor for Western New York, a Regional Meeting of the College members from that district was held in Buffalo, Saturday, March 28, in connection with the Eighth Annual Clinical Day of the Alumni Association of the University of Buffalo School of Medicine. The program began at 9:00 a.m., and consisted of clinical lectures by local and guest clinicians. Dr. Philip S. Hench, F.A.C.P., of the Mayo Clinic was one of these. In the evening the members were the guests at dinner of Governor Russell. It is hoped that this initial endeavor will be expanded and conducted in the future.

REGIONAL MEETING OF GEORGIA MEMBERS

Under the Governorship of Dr. Glenville Giddings, the first Regional Meeting for Georgia members of the American College of Physicians was held on Saturday, March 14. Of a total membership of 83 in the State, 8 of whom are in military

service, 58 members were in attendance. Among the guests were Dr. Fred W. Wilkerson, F A C P, Governor for Alabama, Dr. Turner Z. Cason, F A C P, Governor for Florida, and Dr. Charles Hartwell Cocke, F A C P, Chairman of the Board of Governors and Governor for North Carolina. The program was as follows:

Scientific Session

2 00 p m

Fulton County Academy of Medicine
West Peachtree St

Effects of Sulfonamide Drugs on the Blood	Roy Kracke
Policies of the American College of Physicians	James E. Paullin, President-Elect
Modern Views About the Treatment and Control of Hookworm Disease	Justin Andrews
Pulmonary Edema	Eugene A. Stead, Jr
Military Psychiatry in the Present War	Major Ernest Parsons, Medical Corps, U S A
Blood Replacement Therapy in the Armed Services	Major Douglas B. Kendrick, Jr, Medical Corps, U S A

Dinner

7 30 p m

Capital City Club

Address "Experiences on the Burma Road"
Colonel Louis L. Williams, Jr, U S Public Health Service

Members were most enthusiastic, both about the scientific session in the afternoon and the dinner meeting in the evening, and have endorsed the plan of holding these regional meetings annually.

Dr. Roger I. Lee, F A C P, Boston, Mass., President of the American College of Physicians, addressed the February meeting of the Medical Department Officers residing in Washington, D C, and vicinity at the Steinberg Auditorium of the Army Medical Center, February 16, 1942, on "The Significance and Course of Borderline Abnormalities of Blood Pressure."

Dr. Albert T. Leatherbarrow (Associate), Hampton Station, N B, who was commissioned a Major in the Medical Corps of the Royal Canadian Army, has been appointed Internist at The Lancaster Military Hospital, Saint John, N B.

Dr. Herbert I. Rinkel, F A C P, Kansas City, Mo., was the guest lecturer at the University of Texas School of Medicine, at Galveston, February 23-25, 1942. Dr.

Rinkel spoke on "The Nature and Mechanism of Food Allergy," "Methods of Testing Foods" and "The Clinical Application of Food Principles and Food Tests," and also presented a number of Kodachromes illustrating the "Etiology of Hay Fever in the Mid-West and Southwest."

Dr. Ramon M. Suarez, FACP, San Juan, College Governor for Puerto Rico, will be honored by the Medical College of Virginia at its next commencement. Dr. Suarez will receive an honorary degree of Doctor of Science from the College in recognition of his valuable services to medical science in Puerto Rico.

Dr. Manuel de la Pila Iglesias, FACP, Ponce, has been elected President of the Puerto Rico Medical Association.

Dr. Oscar G. Costa-Mandry, FACP, San Juan, has been appointed Acting Director of the Emergency Medical Services in the Civilian Defense of Puerto Rico.

Dr. Richard A. Kern, FACP, Philadelphia, Pa., was the guest speaker at a recent scientific meeting of the Puerto Rico Medical Association and was unanimously elected an honorary member of the Association.

On January 14, 1942, Dr. Herbert T. Kelly, FACP, Philadelphia, Pa., presented a paper on "The Relationship of Nutrition to Dentistry" at the annual meeting of the Delaware State Dental Society. On March 4, 1942, Dr. Kelly presented a paper on "The Modern Science of Nutrition and Nutritional Deficiency," illustrated with motion pictures in natural color, at a meeting of the Lancaster County Medical Society in Lancaster, Pa.

On February 17, 1942, Dr. Bernard I. Comroe, FACP, Philadelphia, Pa., spoke on "Practical Points in the Management of the Arthritic Patient" at a meeting of the McKean (Pa.) County Medical Society, and on March 19, 1942, he spoke on "The Use of Physical Therapy in Arthritis" at a meeting of the Pennsylvania Academy of Physical Medicine.

Dr. Harry A. Pattison, FACP, Livingston, N. Y., has been awarded a prize for submitting an essay on "Peace After War" in a district contest sponsored by the Rotary Club. Dr. Pattison will award the prize he received to the two students at Hudson High School who write the best essays on the same subject.

On March 19, 1942, memorial services were held at the Harvard Medical School for Dr. Soma Weiss, FACP, Hersey Professor of the Theory and Practice of Physics, Harvard University, and Physician-in-Chief, Peter Bent Brigham Hospital, Boston, who died January 31, 1942. Dr. Walter B. Cannon presided and Drs.

Eugene F Du Bois, F A C P, George R Minot, F A C P, Eugene B Ferris, Elliott C Cutler and William E Watts spoke at the services

Dr George Baehr, F A C P, New York, N Y, is now Chief Medical Officer in the Office of Civilian Defense, Washington, D C

Under the Presidency of Dr Archibald A Barron, F A C P, Charlotte, N C, the North Carolina Neurologic and Psychiatric Association held its regular meeting March 27, 1942, in Charlotte During the scientific session Dr Barron conducted a Clinico-Pathological Conference and Dr Frederick Taylor, F A C P, High Point, N C, participated in the discussion of a series of case reports

The National Tuberculosis Association is conducting during the month of April this year's "Early Diagnosis Campaign" The purpose is to focus people's attention on tuberculosis—to find it, treat it, conquer it More than eight million pieces of printed matter have been prepared and supplied to affiliated associations Some of these publications relate tuberculosis to the Victory effort, for tuberculosis in a community is like so much sand in the production machinery The Association will welcome requests for material from all doctors

Dr Frank F D Reckord, F A C P, Harrisburg, Pa, has been recently appointed the Medical Director of the Harrisburg Hospital

Dr George Herrmann, F A C P, Galveston, Texas, delivered the following addresses during April

'Exigencies of Cardiologial Practice' and "Functional Heart Disorders Including the Soldier's Heart" before the Oklahoma State Medical Association on April 22 and 23, respectively

Some Medical Emergencies and Their Management" and "Military Aspects of the Cardiovascular System" before the Missouri State Medical Association, April 27 and 28, respectively

The First National Congress of Internal Medicine of Mexico will be held May 3-10, 1942, under the Presidency of Dr Teofil Ortiz y Ramirez Dr Francisco de P Miranda, F A C P, and Dr Ignacio Chavez, F A C P, both of Mexico City, are Vice Presidents Dr George Herrmann, F A C P, Professor of Medicine at the University of Texas School of Medicine, Galveston, will present a paper on research work done in the cardiovascular department of the University of Texas

The Eighteenth Scientific Meeting of the American Heart Association will be held June 5 and 6, 1942, at Chalfonte-Haddon Hall, Atlantic City, N J

An intensive course in Tropical Medicine will be given at the New York Post-Graduate Medical School, New York City, for a period of five days, May 25-29, 1942, under the direction of Dr. Z. Bercovitz, F.A.C.P. The course will be a survey of the fundamentals of the various subjects in tropical medicine, and a presentation of the more recent advances that have come from research. Authorities in their respective fields will give lectures and demonstrations in their specialties. Emphasis will be placed on clinical features. Clinical and laboratory material is available for study and demonstration and an opportunity will be given students for practical work in clinical parasitology.

OBITUARIES

DR SOMA WEISS, F A C P , 1928

(This obituary is republished from the *Harvard University Gazette* of March 7, 1942 with their kind permission)

The first shock of the news of the sudden death of Soma Weiss on January 31, 1942, caused among his friends and colleagues the almost universal reaction expressed in words by one, "It is incredible, he was so much alive" Indeed, his vital personality, boundless energy, and excellent health did make him seem to be invulnerable, and his sincere, spontaneous and personal interest in all those with whom he came in contact made his death also the death of something in their lives

He was born in Bestercze, Hungary, on January 27, 1899 During the dark years of the War and of the disintegration of the Austro-Hungarian Empire he attended the Royal Hungarian University at Budapest, where he was appointed Demonstrator and Research Fellow in Physiology and later in Biochemistry In 1920 he came to New York He received the degree of Bachelor of Arts from Columbia in 1921 and only two years later was graduated from Cornell University Medical School as one of its finest products There he came to know Dr Eugene F DuBois as teacher and as a friend through the years While a student he also held an appointment as Assistant in the Department of Pharmacology of Cornell University Working at first under the guidance of Dr Robert Hatcher, he soon published fundamental observations on the reflex nature of the emetic action of digitalis The interest in the action of drugs so acquired was to continue as an outstanding characteristic of his entire subsequent clinical career

After graduation he spent two years as intern at the Bellevue Hospital There he not only received a wide and immediate experience in bedside medicine, but also acquired an understanding of the meaning of that active quality of sympathy for suffering which is expressed by the physician by devoted and intelligent care of the sick In 1925 he joined the group of young physicians attracted by Dr Francis W Peabody to the newly opened Thorndike Memorial Laboratory of the Boston City Hospital From his first days there to the end of his fourteen years at that hospital, he devoted himself whole-heartedly to the success of the Thorndike and its associated teaching services His first appointment in the Department of Medicine was as Research Fellow He rose in only seven years to the rank of Associate Professor—a title perfectly descriptive of his devoted relationship to Dr Peabody's successor, Professor George R Minot In 1932, on Dr Minot's recommendation, Dr Weiss was appointed Director of the Second and Fourth Medical Services In this position his tact and persistence enabled him to make progressive improvements in the clinical services amidst the complexities inherent in the administration of a large municipal hospital In order to draw together in a common interest in medicine and in the City

Hospital the many interns of the Boston University, Harvard, and Tufts Medical Services, he for several years conducted a fortnightly Grand Round, on which were presented and discussed patients of interest from those various services. Thus, his thinking extended beyond the welfare of the Harvard Unit alone and included a vision of the greatness of the City Hospital as well.

Soma Weiss' contacts with his interns and students were especially close. His ward rounds, conferences and lectures were always popular, and his interest in therapeutics was especially welcome to students. His excellent powers of observation, wide clinical and research experience, and knowledge of the American and foreign literatures, allowed him to contribute significantly to any discussion in the laboratory or at the bedside. He was always in demand as a consultant on various of the hospital services and would answer such calls, when necessary, in the small hours of the night with the freshest interest in the problem presented by the patient.

In 1939 Soma Weiss left the City Hospital to succeed Dr. Henry A. Christian as the second Physician-in-Chief to the Peter Bent Brigham Hospital and the eighth of the distinguished line of those who have held the title of Hersey Professor of the Theory and Practice of Physic in the Harvard Medical School. For the post of the Professor of Medicine in the hospital so closely associated with the Medical School he was, because of his many and varied interests, a particularly fitting choice as one who should continue and foster the development of mutually stimulating relationships between these institutions.

Soma Weiss' chief research contributions were in pathological physiology of cardiovascular disease and in clinical pharmacology and therapeutics. They are contained in nearly two hundred publications replete with data especially from painstaking studies on the patients. Dominant in his work was the concept of a mechanism to be proved or disproved. The selection of problems, often suggested by shrewd observation on the wards, seemed to present no difficulty to his active imagination, and his ability to avoid the blind avenues which appear to open so temptingly in the course of experiment, was uncanny. His collaborators included men representative of several branches of medicine, using the word in the broad sense in which he conceived it: pathology, roentgenology, physiology, neurology, surgery, biochemistry and obstetrics. His predominant and constant activity in making original observations rendered him loath to take the time to write summary articles or books. He did, however, contribute a few chapters to systems of medicine, and shortly before his death published, with Dr. Lewis Dexter, a comprehensive monograph on the toxemias of pregnancy. He took the keenest of interest in the intellectual development of the young men who came to work with him. Today many of them hold important posts in academic medicine in this country and abroad.

Men like Soma Weiss do not exert an influence on their fellows by their

ideas alone. Thus, his self-reliance, kindness, enthusiasm for living, and sense of humor were felt by all who knew him. These qualities may have been the result of his having lived on two continents, seen much of sickness and misfortune, and found many friends. He took a deep satisfaction in the life of his family, who enriched the sense of welcome felt by the many friends and strangers invited to his home. His death at forty-three terminated a career short in years but long in terms of accomplishment. Soma Weiss' contributions to medicine are spread upon the permanent record of the literature of medical science, but his true memorial is in our hearts.

W B C

R F

E A S, JR

DR ROCK SLEYSER

Dr. Rock Sleyster, F A C P, Wauwatosa, Wis., was born at Waupun, Wis., June 14, 1879. He attended local public schools and thereafter entered the University of Illinois College of Medicine, graduating in 1902. He entered the practice of medicine at Kiel and Appleton, Wis., and then became physician to the Prison for the Criminal Insane at Waupun, where he did research, much of it reported later in medical periodicals. In 1903 he became Secretary of the Calumet County Medical Society, continuing for six years, and from that time forward was continuously associated with organized medicine and numerous medical societies. In 1910 he became Assistant Secretary of the State Medical Society of Wisconsin, serving four years, then becoming Secretary. In this post he continued until elected President in 1924. The next year he became Treasurer, serving for many years. Dr. Sleyster was Editor of the Wisconsin Medical Journal from 1918 to 1923, Delegate to the American Medical Association, 1913-1914 and 1918-1926, Vice Speaker of the House of Delegates of the American Medical Association, 1922-1926, Trustee, 1926-1937, Acting Chairman of the Board, 1935-1937, President, 1939-1940.

Dr. Sleyster was Medical Director of the Central State Hospital for Insane, Waupun, 1909-1919, Medical Director, Milwaukee Sanitarium, 1919 to the time of his death, during World War I. Major, Medical Corps, U. S. Army, Medical Aide to the Governor of Wisconsin, Chief of the Bureau of Postgraduate Medical Instruction, University of Wisconsin Extension Division, 1916-1920, member, American Psychiatric Association, Association for Research in Nervous and Mental Diseases and the Central Neuropsychiatric Association. He had been a Fellow of the American College of Physicians since 1924, serving as the College Governor for Wisconsin from 1926 to 1940. He died March 7, 1942, at his home in Wauwatosa, Wis., of heart disease, aged 62.

Personal relations of friendly intimacy conceivably do influence fair judgment, and may create a bias in favor of one's thesis. I confess to a

bias when endeavoring to put into words any characterization of a man so gifted, a friend so loyal, a personality so rarely lovable, as was Rock Sleyster.

It was during my incumbency in the editorial management of *The Wisconsin Medical Journal* that attention was first focused upon the secretary of a small upstate county medical society. He leaped into prominence by editing a column that early demonstrated traits that brought him to the forefront in later years: a ripe, understanding nature, a sincere devotion to and student of his fellowman, a mind of rare judicial maturity—instinctive rather than acquired—all rare qualities in one so young, but qualities that constituted the keystone of his later success in institutional management. He was ideally cast in the latter rôle for here was his opportunity to capitalize these qualities, coupled with organizational capacity that followed his career to its zenith.

The Presidency of the American Medical Association was greatness thrust upon Dr. Sleyster, an honor not of his seeking. The office sought a man who could control the confidence of the entire profession—this at a time when matters of far-reaching importance were at stake. And the choice was an uncontested one—a rare expression of professional unanimity for a post of national importance.

Rock's organizational ability, as shown in national affairs, was equally exhibited in the home institution which he created and guided so successfully, and nothing could be a more eloquent tribute than the loyalty with which his staff of associates reciprocated their leader's inspiration. He lived to witness the fruition of the ideal to which he had dedicated the years of his productivity, and though in later years physically incapacitated from as full participation in affairs as he may have wished, he guided in his quiet unobtrusive way, with a steady hand, and a mind alert to the end. Fittingly expressed is Emerson's "An institution is the lengthened shadow of one man."

I might stress another angle of Rock's character that reflects the unique position he had won in this community: his advice was being constantly sought by medical friends from far and near, and he lent a ready ear to such requests—flattered but pleased because these advances evinced a confidence in his integrity of thought and sincerity of action that are the allotted boast of few men. What memorial is more to be cherished than the knowledge that one has gained the respect, the esteem, and the love of his fellowmen?

Rock Sleyster's death was a shock to those who enjoyed his intimate contact and friendship, his lovable character is a happy memory, his influence on his surroundings remains as an enduring monument to his greatness.

ARTHUR J. PATEK, M.D., F.A.C.P.

DR. MARTHA TRACY

One of the most distinguished members of the medical profession, Dr. Martha Tracy, passed away on Sunday, March 22, at the Woman's Medical College Hospital.

Dr Tracy, born in Plainfield, N J , in 1876, attended Plainfield Seminary, Bryn Mawr College, the University of Pennsylvania and Woman's Medical College of Pennsylvania. She attained, through her contributions to the profession and her unflinching interest in organized medicine, a position of honor and esteem not only in Philadelphia but throughout the entire nation. This outstanding woman never, throughout her entire career, failed to answer the urgent call of her chosen field whether as scholar, teacher or public health official.

Dr Tracy served as Associate Professor of Chemistry at the Woman's Medical College from 1909 to 1913, at which time she assumed Professorship of Physiological Chemistry until 1921. From 1921 until 1923 she served as Professor of Hygiene and then became Professor of Preventive Medicine until 1931. This great medical school advanced under her dignified and learned leadership during the time she served as Dean from 1918 to 1940.

In 1940 Philadelphia was most fortunate in having Dr Tracy accept the position as Assistant Director of Public Health. Prior to her position as Assistant Director of Health, Dr Tracy served for many years as Director of the Philadelphia Health Council and Tuberculosis Committee.

Since 1923 Dr Tracy has been a Fellow of The American College of Physicians, always keenly interested in its activities. She likewise served the Philadelphia County Medical Society, the Medical Society of the State of Pennsylvania, the Medical Women's National Association and the College of Physicians in Philadelphia.

It is with much sorrow and regret that we acknowledge the passing of this most beloved friend of medicine.

EDWARD L. BORTZ, M D ,
Governor of Eastern Pennsylvania

DR LEROY S. PETERS

One of the most highly respected and best loved physicians of our State passed away December 17, 1941, as a result of a coronary occlusion.

Dr Peters was born April 6, 1882, at St. Joseph, Michigan. He graduated from the public schools at St. Joseph and took his academic work at the University of Minnesota. He received his medical degree at the University of Illinois College of Medicine in 1906.

Dr Peters came to New Mexico in 1909. He came as did many of the medical profession, with pulmonary tuberculosis, hoping to be benefited by the climate. He regained his health at Silver City, and when he was able to work he began as Assistant Medical Director of the Cottage Sanatorium in that city. In 1913 he came to Albuquerque and was associated with the late Dr. A. G. Shortle as Director of the Albuquerque Sanatorium; he was later Director of St. Joseph's Sanatorium. He was on the active staff of St. Joseph's and the Presbyterian Hospitals from the time the staffs were first organized. He was a Director of the National Tuberculosis Association.

for many years, he was past President of the American Sanatorium Association and the Southwestern Medical Association. He had served as President of his County and State Societies. He was a Licentiate of the American Board of Internal Medicine, and a Fellow of the American College of Physicians since 1927, serving as Governor for New Mexico since 1931.

Dr. Peters was the author of many published papers and was one of the outstanding authorities on pulmonary conditions in the country. He was an indefatigable worker and it was due to the efforts of men like him that we saw the great fall of the death rate of tuberculosis during his period of activity. He attended all medical meetings of the organizations to which he belonged, and was guest speaker at many others.

His wife and one son survive him.

MELDRUM K. WYDLER, M.D., F.A.C.P.

DR. FRANK LEECH

Dr. Frank Leech, F.A.C.P., long a prominent pediatrician, Life Member and former President of the Medical Society of the District of Columbia, died February 4, 1942, at Walter Reed General Hospital, following a long illness. Funeral services were held on February 10 with the Rev. Dr. Frederick Brown Harris of Foundry Methodist Church, and Dr. Leech's brother, the Rev. H. Bishop Leech of Paterson, New Jersey, officiating.

Dr. Leech was born in Prince Georges County, Maryland, on January 14, 1870, the son of the Rev. Dr. George Vanderlip Leech. He attended St. John's College at Annapolis and Ohio Wesleyan University. He received his medical degree from Columbian University, now George Washington, in 1891, and served his internship at Garfield Memorial Hospital where he later became a member of the consulting staff. At Children's Hospital he served in various capacities from 1892 until his retirement in 1938. At that time Dr. Leech was honored by a tablet citing his distinguished services to the institution, and his friends established in his honor the Frank Leech Laboratory Fund.

At the outbreak of the first World War, Dr. Leech volunteered and was commissioned a Major in the Medical Corps. He was placed in charge of the medical departments at Camp Sevier and Fort Sill, Oklahoma. He was later commissioned a Lieutenant Colonel in the Medical Reserve Corps. He held memberships in the Reserve Officers Association, the Military Order of the World War, and the American Legion.

Dr. Leech was Past President not only of the Medical Society of the District of Columbia, but of the Clinico-Pathological Society of Washington. He was a member of the American Medical Association, the Southern Medical Association and the George Washington Medical Society. He had been a Fellow of the American College of Physicians since 1923. He was one of the founders of the American Academy of Pediatrics.

In the death of Dr. Frank Leech the Medical Society of the District of

Columbia has lost a member who was replete with medical knowledge and seeped with the wisdom of experience

Dr Leech had an exceptional capacity for sustained friendship—a friendship constant, without variation or shadow of turning To experience the richness of his companionship was a joy

He met the issues of life unafraid, resolving its complexities into simple formulae He wove the multicolored tapestry of life into the concrete realities of every day

His enduring qualities were love and service Never loosening his hold of the magnetic chain of humanity, he made barren places fruitful with kindness

EDWARD Y DAVIDSON, M D

DR ISADORE JULIUS WOLF

Dr Isidore Julius Wolf, of Kansas City, Missouri, died December 17, 1941, of cerebral hemorrhage Dr Wolf was born in Stuttgart, Germany, and was graduated from the University of Munich and Heidelberg, 1887 He came to Kansas City in 1888, took postgraduate work at the Chicago Post Graduate School in 1889, and later did postgraduate work at the New York Post-Graduate Medical School and at the University of Vienna From 1895 to 1905 he was successively Instructor in Bacteriology, Instructor in Medicine and Professor of Medicine at the University Medical College, Kansas City, Missouri In 1905 he became Professor of Medicine at the University of Kansas School of Medicine He retired about two years before his death and upon his retirement was made a Professor Emeritus For many years he was Head of the Medical Department of the Alfred Benjamin Dispensary, and a member of the St Joseph Hospital staff, he was a member of the Menorah Hospital staff, serving as President of that staff in 1938, and consulting Physician to the Kansas City General Hospital He was a member of the Jackson County Medical Society and Missouri State Medical Society, and had been an Associate of the American College of Physicians almost since its inception Dr Wolf enjoyed a large practice for many years and wrote two books, "The Human Fuel" and "A Family Doctor's Note Book" He retired from active practice several years ago on account of failing health

Dr Wolf is survived by his wife, Mrs Leah Marks Wolf, and three sons, Robert L Wolf, Dr Jack W Wolf and I James Wolf

A. C. GRIFFITH, M D, F A C P,
Governor for Missouri

ANNALS OF INTERNAL MEDICINE

VOLUME 16

MAY, 1942

NUMBER 5

GOLD SALTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS; A STUDY OF 245 CASES*

By RUSSELL L. CECIL, M.D., F.A.C.P., WILLIAM H. KAMMERER, M.D.,
and FRANCOIS J. DEPRUME, M.D., *New York, N. Y.*

THE use of gold salts in the treatment of rheumatoid arthritis has an interesting and rather unusual history. In 1927 Mollgaard¹ carried out some experiments with gold salts as to their effect on the tubercle bacillus. His results were so interesting that Secher² in Copenhagen undertook to treat tuberculosis in man with gold salts. Some of the French students of arthritis had formulated the theory that rheumatoid arthritis was a form of tuberculous joint disease. It was possibly this concept of the problem which led Forestier³ in 1929 to try gold salts in the treatment of rheumatoid arthritis. About the same time Feldt,⁴ Umber,⁵ and Zimmer⁶ in Germany reported successful results with gold salts in the treatment of arthritis. Early in its career gold therapy met with considerable criticism. As Tegner⁷ says "A disease of unknown etiology was being treated with a drug of unknown action, but of very widely known toxic properties," on the slim assumption that there was a possible connection between tuberculosis and rheumatoid arthritis. However, shortly after the publications by Forestier³ and the German investigators, Slot and Deville⁸ in England confirmed the observations of these writers, and since then a number of important reports have appeared in the English and French literature.

In 1934 Forestier,⁹ in his Hunterian lecture, summarized his results with gold therapy in 500 cases of rheumatoid arthritis. In this report he discusses the various forms of gold salts and concludes that for practical purposes gold sodium thiomalate (Myochrysine) and gold thioglucose (Solganal-B) are the most satisfactory agents. Of the 500 cases treated 70 to 80 per cent responded well to gold therapy. Fifty per cent of early cases,

* Received for publication November 24, 1941.

From the Medical Service of the New York Hospital and the Department of Medicine of Cornell University Medical College, New York City.

but only 25 per cent of cases of more than two years' duration, were permanently relieved. In this article Forestier reported his first fatality from gold therapy, a case of agranulocytosis.

In 1935 Hartfall and Garland¹⁰ made their first report on 100 cases of rheumatoid arthritis, nearly all of which had been treated with gold sodium thiosulfate intravenously. The most noteworthy feature of this report was that 45 per cent of the patients had toxic reactions, three patients in the series died, one from agranulocytosis, two from hemorrhagic purpura. One of the deaths from purpura occurred after only five injections of gold salt (total dosage 0.36 gm). Hartfall and Garland reported either cure or marked improvement in 68 per cent of their cases.

In 1936 Forestier and Certonciny¹¹ made an interesting study on 50 cases of rheumatoid arthritis who had received at least four courses of gold and who had been observed for at least three years. They divide their cases into a "small dose" series and a "large dose" series (that is, small and large individual doses). In the small dose series, 70 per cent obtained good results. In the large dose series the results were satisfactory in 50 per cent. The authors explain this apparent inconsistency by noting that large doses were usually given only to severe cases. In 64 per cent of this series the results were excellent (cures or near cures). In 28 per cent the results were only fair, in 8 per cent, negative. In the early cases (less than one year's duration), approximately 75 per cent obtained excellent results. Forestier and Certonciny found that the patients who had recovered and had no relapse all showed a normal sedimentation rate after treatment, furthermore, that patients who recovered but later relapsed always showed an increase in the sedimentation rate during the relapse. In this group of 50 cases who had been observed over a period of three years, 46 per cent had relapses.

In 1937 Hartfall, Garland and Goldie¹² published the largest series so far reported in the literature, a study of 750 cases of rheumatoid arthritis, all of whom received gold therapy. These authors used the commoner gold salts now on the market, but found nothing to choose between them so far as therapeutic value was concerned. However, because of the trouble which they had encountered in their earlier study, they reduced the total dosage of gold salt from 2 gm to 1 gm, and gave the patients a rest interval of three months between courses. In this large series of cases, the authors obtained either cure or marked improvement in 66.7 per cent of the cases. Relapses occurred in 21 per cent of the series, 41.9 per cent had toxic reactions. The latter were severe, however, in only 6 per cent. In this study there were seven deaths (0.78 per cent) due to gold salts, three due to hemorrhagic purpura; one due to agranulocytosis, two due to subacute necrosis of the liver; and one due to exfoliative dermatitis.

In 1937 Copenman and Tegner¹³ stated that of 51 cases of rheumatoid arthritis treated with gold salts, 58 per cent were cured or greatly improved, whereas 18 per cent showed slight or moderate improvement.

In 1938 Ellman and Lawrence¹⁴ reported a carefully controlled series of 52 cases of rheumatoid arthritis, 32 of whom were treated with Solganal-B Oleosum, whereas 20 received only injections of almond oil. These authors reported one fatality from hemorrhagic purpura with associated agranulocytosis. They insisted that toxic reactions were most likely to occur in patients with a normal sedimentation rate. They advised, therefore, only small doses of gold when the sedimentation rate reaches normal. In a follow-up study published in 1940, Ellman, Lawrence and Thorold¹⁵ reported on 90 cases, which they divided into three groups of 30 each. One group received Solganal-B in doses of 0.2–0.3 gm weekly. The second group received 0.1 gm weekly of Solganal-B. The third group received only sterile almond oil. Treatment was continued for a period of nine months in each case. Of the cases treated with large doses of gold, 47 per cent became inactive within nine months. Of those who received small doses, 27 per cent became inactive. In the control series only 3 per cent became inactive. By "inactive" the authors meant freedom from joint pain and a normal sedimentation rate. These authors again stressed the importance of the sedimentation rate as a guide to treatment and claimed that out of a total of 25 cases of gold intoxication, 96 per cent occurred in the presence of a normal sedimentation rate. Recurrence was not encountered among patients in whom the disease had been rendered completely inactive.

In America there has been comparatively little published on the subject of gold therapy in rheumatoid arthritis. In 1939, however, two articles appeared, one by Key, Rosenfeld and Tjoflat,¹⁶ and the other by Snyder, Traeger and Kelly.¹⁷ Key and his co-workers gave myochrysine to 70 patients with arthritis, 53 of whom were rheumatoid cases. Of the 70 cases, 44 had toxic reactions, but there were no deaths. In the 53 cases of rheumatoid arthritis treated with gold salts, 20 (38 per cent) were either arrested or showed marked improvement. These authors consider gold salts particularly valuable in early cases.

Snyder, Traeger and Kelly¹⁷ treated 50 cases of rheumatoid arthritis with gold salts but obtained satisfactory results in only 12 per cent of the cases. These figures are quite at variance with those reported by most other investigators.

PHYSIOLOGICAL EFFECTS OF GOLD

The mechanism by which gold salts act in rheumatoid arthritis is not understood. A number of theories have been proposed. Kling, Sashin and Spanbock¹⁸ thought that the bactericidal effect of gold salts was negligible. They found that in experimental animals gold is deposited in high concentration in the synovial membrane, and they concluded that the efficiency of gold salts in rheumatoid arthritis is probably due to the stimulation of the general reticuloendothelial system, as well as to the effect of the local deposit of gold on the defense mechanism of the synovial membrane. Feldt⁴

thought that in acute and chronic infections the most effective gold compounds were those which contained a sulfur radicle. With such agents he was able to control syphilis in rabbits with an efficiency equal to that of salvarsan.

More recently, Dawson and Hobby¹⁹ have shown that gold salts possess marked chemotherapeutic properties against hemolytic streptococcal infections in mice. The authors remark that the effect was comparable to that obtained with the sulfonamide derivatives. Gold sodium thiomalate had a marked bacteriostatic effect in vitro against the *Streptococcus hemolyticus* at a 1:10,000 dilution.

Sabin and Warren²⁰ have studied the effect of gold compounds on experimental arthritis in mice, which they produced by intravenous injection of pleuropneumonia-like organisms. Various gold salts were found to exert a definitely curative effect on this disease, and the earlier the treatment was begun, the more complete and rapid was the therapeutic response.

Rothbard, Angevine and Cecil²¹ have investigated the effect of gold sodium thiomalate on experimental hemolytic streptococcal arthritis in rats. In this study the authors found that gold sodium thiomalate is an effective chemotherapeutic agent in the prevention of arthritis produced by the hemolytic streptococcus, but that it does not cure the disease once it is established.

Some interesting studies have recently appeared on the fate of gold when injected into the human body. Freyberg, Block and Levey²² injected various gold salts into human subjects and studied their rate of absorption and excretion. These authors found that about 75 per cent of gold was retained in the body during a course of gold therapy, whereas the other 25 per cent was excreted for the most part through the urine, a small fraction through the feces. The gold salt continues to be excreted for weeks, even months, after the injections have been concluded. The authors suggest that the slow excretion of gold salts may explain the serious toxic effects which they sometimes produce on various organs.

Hartung²³ has recently shown that subcutaneous injections of gold salts are followed by a marked increase in the bacteriostatic power of the patient's serum against the hemolytic streptococcus. These effects are in direct proportion to the amounts of gold administered. In view of the demonstrated bacteriostatic power of gold salts, one would naturally expect the serum of treated patients to possess this quality.

PRESENT STUDY

The senior writer of this report began working with gold salts in the treatment of rheumatoid arthritis in 1933, shortly after the visit of Forestier to this country. We had treated only a few cases, however, before we ran into trouble in the form of a severe exfoliative dermatitis. This experience cooled our enthusiasm somewhat, but we continued using gold salts on

selected cases during the following five years. In 1938 we began to use gold intensively, and during the past three years practically all of our rheumatoid cases have received gold therapy.

The present study includes 245 cases of rheumatoid arthritis, all of whom received gold salts. Ten cases of ankylosing spondylitis have been excluded from some of the tables because we felt that they should be considered separately. In this study we have made a particular effort to include only cases of *bona fide* rheumatoid arthritis. Seventy per cent of the patients in the series showed one or more fusiform fingers, and of the remainder practically all presented swollen knuckles, ankyloses or deformities, or other characteristic features of the disease. Of 76 patients who had roentgen-rays of the joints, 80 per cent showed the characteristic radiographic changes. Ninety-five per cent of the series presented an elevated sedimentation rate. Sixty-four per cent of 193 patients gave a positive agglutination reaction to the *Streptococcus hemolyticus*. Eighteen patients, or 7.6 per cent, had one or more subcutaneous nodules. A number of patients who had received gold therapy were finally excluded from this study because of some doubt in our minds as to their clinical identity.

Ninety-two patients were studied in the out-patient department or in the wards of the New York Hospital. The remaining 153 were private patients. Both series, however, received the same work-up and laboratory study. As far as we can see, there is not much difference in the type of patient which one sees in the clinic and in private practice.

Age and Sex. This series contained about twice as many females as males (158 vs 87). The age at onset fell between 20 and 40 years in 40 per cent, and between 40 and 60 years in 43 per cent of the cases.

Degree of Severity. We classified our rheumatoid arthritides according to severity into four groups, as follows:

Group 1 (1+) Mild cases, ambulant. These patients were still able to work every day and had only a moderate degree of swelling and pain in several joints, including usually two or three fingers. Twenty-nine per cent of the patients studied fell into this group.

Group 2 (2+) Moderately severe cases, mostly ambulant. Great majority of more than a year's duration. These patients were usually only partly incapacitated and could do certain kinds of work. They invariably presented a multiple arthritis with well established changes in the hands, wrists, knees and other joints. This was our largest group, constituting 57 per cent of the total series.

Group 3 (3+) Severe cases, only partially ambulant. Many of these patients were treated as bed patients during part of the period of observation, either in the home or in the New York Hospital. Thirteen per cent fell into this group.

Group 4 (4+) Very advanced type of rheumatoid arthritis, totally crippled, unable to walk. There were only two cases of this type included in the series.

Our material is also classified according to the duration of disease. All patients were divided into early and late cases, early cases being those who had had arthritis not more than one year, late cases being those who had had arthritis for more than one year. The late cases outnumbered the early cases by almost three to one (170 to 65).

Ten patients in the series presented the picture of ankylosing spondylitis of the Marie-Strumpell type.

Two cases occurred in children under 10 years of age and were classified as Still's disease. It is now generally recognized, however, that Still's disease is nothing more than juvenile rheumatoid arthritis.

Associated Diseases Of our cases 42 per cent had psoriasis combined with arthritis and showed the characteristic changes in the finger nails and terminal phalanges.

Eight cases presented the typical signs of rheumatic heart disease. It should be added, however, that because of the chronicity of the joint changes we felt justified in classifying them as rheumatoid arthritis rather than as subacute or chronic rheumatic fever.

Other Forms of Therapy The great majority of patients in this study had had arthritis for a number of years and had tried various forms of therapy, usually without any permanent benefit. The agents that had been most frequently employed were vaccines, vitamins, sulphur, physiotherapy, and removal of foci of infection.

METHODS

Laboratory Methods A complete blood count and urinalysis on patients who were receiving gold therapy were carried out once a month for signs of intoxication. The sedimentation rate of the red blood cells, as determined by the Rourke and Ernstene method, was determined before treatment was started and was repeated every two to three months while gold was being administered. In a few patients frequent platelet counts were made, but they afforded little or no information. The streptococcus agglutination test was made in the majority of instances. In many cases in which the diagnosis was in doubt, roentgen-rays of the joints were taken.

METHOD OF TREATMENT

The present study is concerned primarily with the effect of gold salts on the course of rheumatoid arthritis. However, supplementary therapy in the form of vitamins, physical therapy and streptococcus vaccine was used in certain instances. In evaluating results, however, these forms of treatment were not taken into consideration inasmuch as they have usually been found ineffective in this disease when used either singly or in combination.

With respect to gold salts, we have used only three in this study.*

* We are indebted to Merck & Company, Schering Corporation and Abbott Laboratories for the gold salts employed in this study.

- 1 Gold sodium thiomalate— $C_4H_7O_4SAuNa_2$ —(Myochrysine)—207 cases
- 2 Aurothio-glucose— $C_6H_{11}O SAu$ —(Solganal-B Oleosum) — 40 cases
3. Gold sodium thiosulfate— $Na_2Au(S_2O_3)2H_2O$ — 3 cases

There were a few instances in which the same patients received both myochrysine and Solganal-B. Myochrysine and Solganal-B were administered intramuscularly into the buttock. Gold sodium thiosulfate was given intravenously. In all cases the gold injections were administered once a week.

Dosage The usual plan was to start the patient on 10 mg of the gold salt and work the dose up gradually to 50 or 100 mg. Occasionally patients who did not respond to these doses were given 200 mg injections, but this was exceptional.

Our material can be roughly divided into two groups. (1) Large dose series, in which the patient received weekly injections of 100 mg of gold salt until he had taken 1–1.5 gm of the drug. There were 151 cases in this group. (2) Small dose series. The maximum dose in this series was 50 mg administered once a week. These patients received a total of 5–1 gm of gold salt. The number of cases in this group was 63. A small group of 11 patients received a mixture of small and large doses. These figures do not include 38 patients who received inadequate treatment nor the 10 cases of ankylosing spondylitis.

Total Dosage of Gold Most writers on gold therapy have advocated the administration of gold in courses, each course to consist of a total dosage of 1 to 1.5 gm. Most patients require at least two courses, and many have to have four or five, or even more.

In our investigations on gold therapy we followed the usual rule of allowing an interval of six to eight weeks to elapse between courses of gold therapy. However, in the cases of patients who developed toxic reactions gold was immediately discontinued, sometimes temporarily, sometimes permanently.

In table 1 we have classified our cases according to total dosage of gold salts. Forty-one, or 16 per cent, of our patients received a total dosage of less than 0.5 of a gram, which we considered inadequate therapy. Not all of these discontinued gold, however, on account of an intolerance for the drug, as will be pointed out later.

TABLE I
Total Dosage of Gold Salts in 245 Cases of Rheumatoid Arthritis

Amount	Cases	Per Cent
Less than 0.5 gm	41	17
0.5–0.9 gm	63	26
1.0–3.0 gm	116	47
Above 3.0 gm	19	8
Amount Questionable	6	2
Total	245	

In table 2 our cases are classified according to the number of courses of gold therapy which they received. The number can be roughly divided between 107 who received only one course, and 90 who received two or more courses. It should be added that many of the patients who are listed in this

TABLE II
Courses of Gold Salts in 197 Cases of Rheumatoid Arthritis *

Number of Courses	Cases	Per Cent
One	107	54
Two	53	27
Three or More	37	19
Total	197	

* 38 cases of inadequate treatment excluded 10 cases of ankylosing spondylitis excluded

table as having only one course are now receiving their second or third course. Most authorities have insisted that every patient, no matter how successful the results with the first course of gold, should receive at least two courses to prevent a possible relapse.

RESULTS OF TREATMENT

The authors have devoted a good deal of thought to the question of how the results should be classified. We finally adopted in part the terminology of Ellman and Lawrence, who described those patients who became free of all swelling and pain as "remissions." The term "inactive" would be equally applicable. To speak of a "cure" would be unsuitable because, as in the case of tuberculosis, a considerable number of arthritics relapse. On the other hand, we think it is a mistake to follow the terminology used by certain European writers and speak of these apparently cured cases as "greatly improved," a term which does not adequately describe their status. We have, therefore, decided to classify our cases as follows:

(1) **Remissions** Patients who become free of all pain and swelling, although they may have some residual deformities, such as one or two ankylosed fingers, and who are again able to do a full day's work. Most patients in this group have a normal or only slightly elevated sedimentation rate at the time of their remission.

(2) **Greatly Improved** Patients who still have some swelling and pain, but are able to work for at least part of the day. Sedimentation rate usually reduced, but not often normal.

(3) **Moderate Improvement** The patients in this group show some improvement from gold treatment, but the results are not convincing. The improvement is of the type which any arthritic might undergo spontaneously.

(4) **No Improvement**

In table 3 the gross results of treatment with gold salts in 235 cases of rheumatoid arthritis are listed. Thirty-one per cent of those receiving adequate therapy had a complete remission with respect to pain and swelling in

TABLE III
Results with Gold Therapy in 235 Cases of Rheumatoid Arthritis *

Result	Cases	Per Cent
Remission	62	31
Greatly Improved	68	35
Moderately Improved	39	20
No Improvement	28	14
Total	197	
Insufficient Treatment	38	
Total	235	

* 10 cases of ankylosing spondylitis excluded

the joints. Thirty-five per cent showed marked improvement. Combining these two groups, 66 per cent either became inactive or were greatly improved. This figure checks closely with the 66.7 per cent of Hartfall and Goldie and the 68 per cent of Forestier, who showed either remission or marked improvement. The remaining third of the cases were either only moderately improved or showed no improvement at all.

In table 4 we have summarized the results of gold therapy in relation to the duration of the arthritis. This table indicates the advantage of gold therapy early in the disease. Thirty-nine per cent of the cases treated early

TABLE IV
Results with Gold Therapy in Relation to Duration of Arthritis

Result	Early Cases	Late Cases
Remission	20 (39%)	42 (29%)
Greatly Improved	20 (39%)	48 (33%)
Moderately Improved	5 (10%)	34 (23%)
No Improvement	6 (12%)	22 (15%)
Total	51	146
Insufficient Treatment	13	25
Total	64	171

had remissions as compared with 29 per cent of the late cases. Thirty-nine per cent of the early cases showed great improvement as compared with 33 per cent of the late cases. Altogether, 78 per cent of the patients treated early showed either complete remission or great improvement.

When the results of gold therapy were analyzed in relation to the severity of the disease, the percentage of remissions and great improvement were found to be just about the same in the mild and in the severe cases, namely 63

versus 67 per cent. However, these figures are not as inconsistent as they might at first appear. It has long been recognized that the severe fulminating type of arthritis often responds better to treatment than the comparatively mild, indolent form.

A further analysis of the remissions indicates that 77 per cent of them had a total of one gram or more of gold salt, whereas only 41 per cent of those who showed no improvement had a total dosage of one or more grams.

In this connection it is interesting to analyze the 38 cases who had insufficient treatment with gold salts. We were curious to know how many of these patients stopped the treatment because of reactions, and how many for other less important reasons. The following figures throw some light on this question.

Of the 38 cases who received inadequate gold therapy, 19, or 50 per cent, discontinued the treatment because of toxic reactions. Nine stopped because of failure to show immediate improvement. The two cases of juvenile rheumatoid arthritis received only small doses of gold, and in the eight remaining cases the cause for discontinuance could not be determined. We wish to stress one point, however, and that is that many patients, even those who have had severe reactions, can, after a sufficient rest period, take further gold treatment without any complications. In such patients, however, it may be wise to limit the maximum individual dose to 25 or 50 mg.

Ankylosing Spondylitis We have treated 10 cases of ankylosing spondylitis with gold salts. Three received inadequate treatment. Of the remaining seven there was only one patient who improved. This type of arthritis appears to be refractory to gold treatment.

Still's Disease Two children with Still's disease were treated with gold salts. Because of their age, small doses (not over 25 mg) were used and the total dosage was not carried above 0.5 gm. One child had a complete remission following gold therapy, which has lasted over five years. The other child is still under treatment and has shown moderate improvement. In this latter case it was necessary to interrupt treatment because of a tendency to thrombocytopenia. However, she was subsequently able to tolerate small doses of gold satisfactorily.

Effect of Gold Treatment on the Sedimentation Rate Much has been written concerning the effect of gold therapy on the sedimentation rate, and all are agreed that in patients who respond well to gold therapy, the sedimentation rate is reduced and in many cases actually reaches normal. As mentioned above, 95 per cent of our patients showed an elevated sedimentation rate before gold treatment was instituted. In the group of patients who had remissions after gold therapy, 47 per cent of those with a high sedimentation rate developed a normal or only moderately elevated sedimentation rate. In contrast to this group, of those who showed no improvement under gold therapy, only 5 per cent with a high sedimentation rate showed a striking reduction after gold therapy. If one includes only those patients whose sedimentation rate actually reached normal, the contrast is even more striking,

37 per cent of the patients in the remission group developed a normal sedimentation rate after gold treatment, whereas not a single case in the "no improvement" group developed a normal sedimentation rate after treatment.

We have not been able to determine the factors which are essential in obtaining a remission. All we can say from a survey of our material is that a majority of the patients who had remissions were treated early, received a larger total dosage of gold, and showed a rather rapid drop in the sedimentation rate. It is also interesting to note that 53 per cent of the remissions had some form of toxic reaction to gold, as compared with 42 per cent for the entire series. Age, sex and severity of the disease do not appear to be determining factors.

Relapses Comparatively little has so far appeared in the literature on gold therapy concerning the prevention and treatment of relapses. Unfortunately, relapses are quite a common occurrence and detract a great deal from the efficiency of gold therapy. In table 5 we have indicated the in-

TABLE V
Incidence of Relapse after Treatment with Gold Salts

Result of Gold Therapy	Cases	Relapses	Per Cent
Remission	62	21	34
Greatly Improved	68	34	50
Moderately Improved	39	13	36

cidence of relapses in patients treated with gold salts. Thirty-four per cent of the remissions, and 50 per cent of the "greatly improved" patients relapsed. Most relapses come on within six to 12 weeks after gold therapy has been discontinued. We have seen relapses occur, however, as late as one or two years after remission. There is general agreement among writers on gold therapy that relapses are milder than the original attack. The symptoms usually reappear in the same joints and are most likely to occur in patients whose sedimentation rate remains high in spite of striking improvement.

Our investigations indicate that the great majority of patients get the maximum benefit of gold therapy from the first course. Many of those who relapsed again showed remissions or great improvement after further treatment, but improvement was rarely more marked than with the original course of gold treatment. Fifty per cent of the remissions who relapsed became inactive again after further gold therapy, and 66 per cent of the greatly improved group who relapsed were greatly improved once more by a second course of gold therapy. Only two patients in the greatly improved group who relapsed had a remission following the second course of gold therapy.¹ In the moderately improved group there were 13 relapses, and further gold treatment did not elevate any of these patients into the remission or greatly improved groups. However, our statistics indicate that a considerable percentage of patients who relapsed again had remissions or great improvement following a second course of gold treatment, for in the final

analysis 50 per cent of our cases, in spite of relapses, achieved a successful result, i e, either a remission or great improvement

Duration of Remissions In table 6 we have indicated the duration of remissions following gold therapy up to the time of the conclusion of our

TABLE VI

Duration of Remissions in 50 Cases of Rheumatoid Arthritis Treated with Gold Salts

Duration of Remission	Number of Cases	Per Cent
Less than 6 Months	10	20
6 Mos -1 Year	14	28
1-2 Years	16	32
2-5 Years	8	16
Above 5 Years	2	4
Total	50	

experiment on February 1, 1941 It is interesting to note that in this table remissions have lasted more than a year in 52 per cent of the cases

Toxic Reactions These reactions are listed in table 7 The incidence of toxic reactions was 42 per cent, a figure which checks closely with that of

TABLE VII

Toxic Reactions to Gold Salts in 245 Cases of Rheumatoid Arthritis

Exfoliative Dermatitis	11
Other Skin Lesions	52
Stomatitis	13
Gastrointestinal Symptoms	18*
Jaundice	2
Purpura	3
Agranulocytosis	1
Bronchitis	2
Albuminuria	3
Total	105

* One case of ulcerative enteritis died

some of the preceding studies In estimating the number of toxic reactions we have not included the immediate nitritoid reactions which we obtained with certain lots of inyoehrysin and which now, fortunately, have been eliminated. In this table we have placed exfoliative dermatitis first because it is the most prevalent of the severe reactions As a matter of fact, in those patients who had localized exfoliative dermatitis, the condition was not severe, but quite uncomfortable Four patients, however, with generalized exfoliative dermatitis had to be hospitalized It is interesting to observe that four out of our 11 cases of exfoliative dermatitis developed a rash after a total dosage of less than 0.5 gm of gold salts Of the patients who developed exfoliative dermatitis, nearly all showed marked improvement in their arthritis during and following the dermatitis, although some relapsed later

The next most common skin lesion was *squamose dermatitis*. This usually cleared up fairly promptly after discontinuance of gold.

Other less frequent skin lesions were erythema, herpes zoster, herpes labialis, folliculitis, dermatitis pigmentosa and furunculosis.

Stomatitis was fairly common but rarely caused the patient much annoyance. A few patients lost their sense of taste for a short time.

Gastrointestinal symptoms were usually mild, consisting of nausea, colicky pains and diarrhea. One patient, aged 70, following her first injection of myochrysine, developed an ulcerative enteritis (confirmed by autopsy) from which she eventually died. We were not convinced, however, that this patient's death should be attributed to the gold injection. In the first place, she had had symptoms of intestinal trouble for years. In the second place, she had received only one injection of 25 mg of myochrysine. There is no record of anyone's developing a fatal gold intoxication from such a small dose of gold salt.

Two patients in our series had jaundice but both made an uneventful recovery. It was interesting that both of these patients had a temporary remission of their joint symptoms during, and for a few months following their attack of jaundice, thus corroborating the observations of Hench and others that jaundice is frequently followed by a temporary cessation of arthritic manifestations.

Three of our patients developed purpura, but this cleared up promptly when gold was discontinued. Two out of the three cases of purpura occurred after less than 0.5 gm of gold. One patient had an agranulocytosis, accompanied by intense angina, but recovered.

"Gold bronchitis" occurred twice, marked albuminuria in three cases. One of the patients who developed albuminuria showed many granular and hyaline casts, but this eventually cleared up almost entirely, and there was no evidence of impaired renal function.

We have been unable to determine what factors are responsible for toxic reactions in some patients and not in others. Furthermore, we have found no effective means of prevention or treatment.

DISCUSSION

Joseph Miller's famous remark about "the inevitable 70 per cent" of rheumatoid patients who improve under almost any kind of treatment has been much quoted. Spontaneous remissions, of course, do occur in rheumatoid arthritis, but they have been extremely rare in our experience and the patient may have to wait several years for the remission. Gold therapy will sometimes induce a remission in as short a period as six weeks.

Forestier and Certonciny¹¹ say that only 1 to 2 per cent of true rheumatoid arthritics make a spontaneous permanent recovery. Remissions, however, even a year or more in duration may occur in 10 per cent of cases. They dispute the statements of Dawson, Bauer and others that 15 per cent of

rheumatoid patients make a complete recovery regardless of treatment. This disagreement indicates the great need for a careful follow-up study, over at least a 10 year period, of patients with rheumatoid arthritis.

Dosage is still an unanswered problem as far as gold therapy is concerned. Sabin and Warren²⁰ found in their studies on experimental arthritis that a better response was obtained with larger doses of the gold compounds. Freyberg and his colleagues believe that the doses which most clinicians use today are unnecessarily large. He bases this opinion on the fact that only a comparatively small amount of the gold injected each week is excreted from the body. It is interesting to note that Secher,² one of the first clinicians to work with gold, used very large individual doses, sometimes equal to the total dosage at the present time. Forestier²⁴ states that of patients who received a total of less than one gram of gold salts, 50 per cent obtained poor results. In our study, we have found that the best results were obtained in patients who received a relatively large total amount of gold salts (1 gram or more). On the other hand, the size of the individual dose did not have a very definite effect on the results of treatment.

Of one thing we are quite convinced, namely, that gold salts are most effective in the treatment of early cases. We are, therefore, in disagreement with Snyder and his co-workers,¹⁷ who say that gold treatment should be undertaken only when the arthritis is refractory to every other form of treatment.

Most authorities believe that a rheumatoid patient should have at least two courses of gold therapy before a decision can be made as to the value of the treatment for that particular patient. Forestier²⁵ states that patients who receive only one series of gold salts will nearly always relapse. He even goes so far as to say that he never saw a permanent cure result from one series of injections. We find ourselves somewhat sympathetic with this point of view, however, we certainly have the impression quite strongly that if the patient receives no benefit at all from his first gold series, he is not likely to obtain a striking result from a second or third course.

Of all the laboratory tests, the sedimentation rate is perhaps the most important as a check on treatment, although monthly blood counts and urinalyses are important as a means of detecting incipient toxic reactions. Forestier² believes that every patient treated with gold should have a coagulation time and a bleeding time before treatment is started, as this would give warning of any tendency toward purpura. However, we are not convinced that this is true.

We agree with Hartfall, Garland and Goldie¹² that although the sedimentation rate is an important guide to treatment, one occasionally sees marked clinical improvement without a drop in the sedimentation rate. Such patients, however, are very apt to relapse a few weeks or months after gold treatment is discontinued. Forestier and Certonciny¹¹ advise that gold treatment should not be stopped as long as the sedimentation rate is high, but the rate cannot be followed literally.

After a number of years' experience with gold therapy we are disposed to look upon the relapse as just as much of a bugbear to successful treatment as are the toxic reactions. To be sure, the relapse is usually milder than the original attack, but on the other hand it does not seem to yield so strikingly to gold therapy as does the first attack. In the present study more than 52 per cent of remissions lasted longer than a year, and a few have lasted even five years.

The physician cannot be too careful in watching for the early signs of toxic reaction. The longer one works with gold, the less difficulty he seems to encounter with toxic manifestations, probably because he learns from experience how to adapt dosage to the particular case and to take heed of the first premonitions of intoxication.

Judging from the literature, the most serious complication of gold therapy is hemorrhagic purpura. This is a rare complication, but its possibility should be always in mind and the number of platelets noted with every blood count. Gasking²⁶ has pointed out that for a few days after each injection of gold the blood platelets show a sharp but temporary drop. When gold is given only once a week, the platelet count returns to normal before the next injection of gold, except when the patient is intolerant to gold. Gasking goes so far as to say that a platelet count should be made before each injection of gold.

We agree with Tegner⁷ in doubting the value of the various agents which have been recommended for the prevention of toxic reactions. An analysis of our toxic reactions would indicate that although the incidence is high, less than 10 per cent of the patients treated by us with gold salts had to discontinue gold therapy permanently because of intolerance to the agent.

In view of the fact that gold is a dangerous form of therapy, the question may well be asked "Is it too dangerous to be used by the general practitioner?" The answer to this question must be qualified. Boots²⁷ advises those who would administer gold salts first to obtain some experience in an arthritis clinic, where gold is being used extensively. This is sound advice, but unfortunately such a procedure is not always feasible. Important things to remember are (1) Use gold only in cases with typical rheumatoid arthritis. (2) Do not give gold to a patient with a history of previous hemorrhagic disease or with any other serious constitutional disease. (3) Start with small doses and work up gradually. (4) Examine the patient carefully every week for skin rash, sore mouth, etc. (5) Examine the blood and urine once a month.

It has been said by more than one writer that gold is the best single agent for the treatment of rheumatoid arthritis. This does not seem to us a sensational statement, especially when one considers how disappointing most other forms of treatment are. Furthermore, there is no reason to believe that gold therapy has reached its maximum efficiency. Sabin²⁸ has recently shown that calcium gold thiomalate is much less toxic for animals than the sodium salt. Eventually some such agent may prove to have all of the

therapeutic value of the present products, with much less toxic quality. It seems reasonable to assume that improvements in the product itself, together with more accurate knowledge concerning the dosage, metabolism and excretion of gold, will enable us to use this agent much more efficiently in the future.

SUMMARY

1 In the present study of 245 cases of rheumatoid arthritis, gold salts when given in adequate dosage caused remission or marked improvement in 62 per cent of the cases. In 10 cases of ankylosing spondylitis, gold salts were beneficial in only one case.

2 Even better results were obtained in arthritics of less than one year's duration.

3 The incidence of toxic reactions was high. They manifested themselves chiefly as dermatitis or stomatitis. There was one fatal case of ulcerative enteritis in this series of cases which possibly may have been due to gold salts.

4 Relapses occurred in 42 per cent of the patients who received marked benefit from gold therapy. The relapses were usually milder than the original attack, but yielded less promptly to gold therapy.

5 Gold therapy can be a dangerous form of treatment and requires close observation of the patient and frequent examination of the blood and urine. In spite of its dangers, however, its beneficial effect on the course of rheumatoid arthritis would seem to justify its use in patients who can tolerate the drug.

REFERENCES *

- 1 MOLLGAARD, HOJGER. Some of the principal questions in chemotherapy with special regard to heavy metals, *Proc Roy Soc Med*, 1927, xx, 787.
- 2 SECHER, K. Behandlung von Gelenkleiden mit Sanocrysin, *Acta med Scand*, 1933, lxxix, 506-521, abstr. *Deutsch med Wchnschr*, 1933, lv, 90-91.
- 3 FORESTIER, J. L'aurotherapie dans les rhumatismes chroniques, *Bull et mem Soc med d hôp de Par*, 1929, lxx, 323. La chrysotherapie dans les rhumatismes chroniques, *Bull et mem Soc med d hôp de Par*, 1929, xlv, 323.
- 4 FEIST, A. Chemotherapeutische Versuche mit Gold, die Wirkungsweise von Goldpräparaten im infizierten Tiere, *Klin Wchnschr*, 1927, vi, 1136.
- FEIST, A., and WEGNER, L. Chemotherapeutische Versuche mit Gold, die Behandlung der Pasteurellainfection mit Goldverbindungen, *Klin Wchnschr*, 1928, vii, 1034.
- 5 UMBER, I. Zur Diagnostik und Therapie chronischer Gelenkerkrankungen, *Med Welt*, 1929, iii, 593 and 633.

* Since this article was written, three important additional reports on gold therapy have appeared in the literature, all of them showing favorable results. The references are as follows:

- 1 SUNDLUND, ERIK. Die Goldbehandlung der chronischen Arthritis unter besonderer Berücksichtigung der Komplikationen, Lund 1941, Kåkar Ohlssons Boktryckeri.
- 2 DAYTON, M. H., DOORS, R. H. and (by invitation) FAYON, I. I. Gold salts in the treatment of chronic arthritis. *Trans Assoc Am Phys*, 1941, lvi, 330.
- 3 DE PRUME, F. J., and KAMMERER, W. H. Tratamiento del Reumatismo por los Sales de Oro. *Revista Médica y Educativa de la Universidad de Buenos Aires*, 1940.

- 6 ZIMMER, A Die Behandlung der rheumatischen Krankheiten, Leipzig, Sacher's Medizinische Buchhandlung, 1930 p 268
- 7 TRIGNER WM Present trend of gold therapy for arthritis in England, Proc Staff Meet Mayo Clin, 1939, vii, 117
- 8 SLOT, G, and DRAHLL, P M The treatment of arthritis and rheumatism with gold, Lancet, 1934, i, 73
- 9 FORESTIER, J Rheumatoid arthritis and its treatment by gold salts, Lancet, 1934, ii, 646
- 10 HARTFALL, S J, and GARIAND, H G Gold treatment of rheumatoid arthritis, Lancet, 1935, ii, 8
- 11 FORESTIER, J, CERTONCINI, and PERIJS La chrysotherapie prolongee dans les polyarthrites Etude de cinquante cas, La revue du rhumatisme, 1936, iii, 485
- 12 HARTFALL, S J, GARIAND, H G, and GOLDIE, W Gold treatment of arthritis, a review of 900 cases, Lancet, 1937, ii, 784, 838
- 13 COFFMAN, W S C, and TRIGNER, W A review of gold therapy, Lancet, 1937, i, 554
- 14 ELLMAN, P, and LAWRENCE J S Gold therapy in rheumatoid arthritis an assessment of its value with control experiments, Post-Grad Med Jr, 1938, vii, 275
- 15 ELLMAN, P, LAWRENCE, J S, and THOROLD, G P Gold therapy in rheumatoid arthritis, Brit Med Jr, 1940, ii, 312
- 16 KEY, J A, ROSENFELD, H, and TJOELAT, O E Gold therapy in proliferative arthritis, Jr Bone and Joint Surg, 1939, xxi, 339
- 17 SANDER, R G, TRAEGER, C T, and KEELY, L Gold therapy in proliferative arthritis, observation on 100 cases treated with gold sodium thiosulphate and aurocein, ANN INT MED, 1939, vii, 1672
- 18 KLING, D H, SASHIN, D, and SPANBOCK, J The mechanism of gold therapy in rheumatoid arthritis, Jr Lab and Clin Med, 1939, xxi, 1241
- 19 DAWSON, M H, and HOBBS, G L Chemotherapy of experimental hemolytic streptococcal infections with gold salts, Jr Pharmacol and Exper Therap, 1940, xix, 359
- 20 SABIN, ALBERT B, and WARREN, J The curative effect of certain gold compounds on experimental proliferative chronic arthritis in mice, Jr Bact, 1940, xl, 823
- 21 ROTHBARD, S, ANGEVINE, D M, and CICIL, R L The influence of gold sodium thiomalate (myochrysin) on the prevention of hemolytic streptococcus arthritis in rats, Jr Pharmacol and Exper Therap, 1941, lxxii, 104
- 22 FREYBERG, R H, BLOCK, W D, and LFEY, S Metabolism, toxicity and manner of action of gold compounds used in the treatment of arthritis 1 Human plasma and synovial fluid concentration and urinary excretion of gold during and following treatment with gold sodium thiomalate, gold sodium thiosulfate, and colloidal gold sulfide, Jr Clin Invest, 1941, xx, 401
- 23 HARTUNG, E F The excretion of gold following the administration of gold sodium thiomalate in rheumatoid arthritis, Jr Lab and Clin Med, 1941, xxvi, 1750
- 24 FORESTIER, J Treatment of rheumatoid arthritis with gold salts injections, Lancet, 1932, i, 441
- 25 FORESTIER, J Rheumatoid arthritis and treatment with gold salts, Jr Lab and Clin Med, 1935, xx, 827
- 26 GASKING, C T The influence of gold salts on the blood platelets in rheumatoid arthritis, Chronic Rheumatic Diseases (C W Buckley), 1938, H K Lewis & Co Ltd, London, No 4, p 106
- 27 BOOTS, R President's address, American Rheumatism Association Meeting, Cleveland, Ohio, June 2, 1941
- 28 SABIN, A, and WARREN J The therapeutic effectiveness of a practically non-toxic new compound (Calcium Aurothiomalate) in experimental, proliferative, chronic arthritis of mice, Science, 1940, xcii, 535

THE MANIFESTATIONS IN THE SKIN AND MUCOUS MEMBRANES IN DERMATOMYOSITIS, WITH SPECIAL REFERENCE TO THE DIFFERENTIAL DIAGNOSIS FROM SYSTEMIC LUPUS ERYTHEMATOSUS¹

By HARRY KEIL, M D , *New York, N Y*

IN dermatomyositis characteristic eruptions are encountered in the skin and mucous membranes. These appearances must always be correlated with the remainder of the clinical picture, yet recognition of them often enables the observer to gain proper orientation in what seems to be an obscure case. Knowledge of these various manifestations provides a more substantial background for an evaluation of the differential diagnosis, therapy and prognosis of a disease that is far more common than the reports in the literature would indicate.¹ Throughout this communication stress will be laid on clinico-pathologic correlations and special reference will be made to the differential diagnosis from systemic lupus erythematosus, a disease that is often confused with dermatomyositis.

For convenience the eruptions observed in dermatomyositis may be classified under the following headings:

1 The characteristic appearances that possess diagnostic importance of more or less significance. These may be subdivided, further, into two groups:

a the lesions that seem to occur independently of the pathologic changes in the muscles and subcutaneous tissues. The net effect produced by these manifestations is that of an exanthematic disease. Under this heading the enanthem as well as a number of "vasomotor" phenomena will also be mentioned.

b the lesions that are related to or are associated with underlying involvement of the muscular and subcutaneous tissues. Generally speaking, these manifestations seem to fall in the category of "collateral inflammatory changes."

2 The dermatoses that show banal or nondescript attributes, for example, "erythema multiforme," vesiculo-bullous elements, purpura, etc. Their occurrence may tend actually to confuse the clinical picture and, whereas they are best remembered for their negative attributes, there are occasional instances in which these prove to be a "revealing" or directing sign.

Any one of these manifestations may be the initial or, at least, an early sign in dermatomyositis.

1a *Eruptions Independent of Underlying Muscular Disease the Exanthem and Enanthem* The sites affected most commonly are the face (eyelids, contiguous parts of the forehead and cheeks, including the "flush area"), ears, oral mucosa and the skin overlying the articulations, especially of the small joints of the hands. Of these the eyelids and the small articulations are the most important sites for diagnosis. Often other parts of the body are affected, such as the V-shaped area of the neck and the nuchal region. In some instances the eruption is generalized ab initio or there is gradual spread over the cutaneous surfaces. As a rule, the palms and soles are spared. In cases with widespread involvement of the skin it is the rule that only a few areas show acute or active alterations, and this is especially true in instances in which the original sites of lesions have disappeared or have been replaced by faint pigmentation. Frequently these lesions seem to pursue a fairly chronic course in the sense that they or their sequelae may remain visible a long time, but exceptions do occur. The attributes displayed by the manifestations falling in this group often vary with the stage of the general disease (acute, subacute, chronic), but there are no absolute rules in this respect owing chiefly to the considerable overlapping of stages (for example, an acute exacerbation during apparent clinical quiescence). In particular, the atrophic lesions to be described afford valuable diagnostic evidence of this disease, notably in its chronic forms (chronic dermatomyositis, some cases of myositis fibrosa, etc.)

In dark-hued persons and in negroes the cutaneous manifestations are perhaps less easily recognized; yet the difficulties are generally more apparent than real, for the clinical picture is usually distinctive.

There are, as a rule, no subjective complaints. Itching or burning of the skin of the face, neck and other parts may occur sometimes, and this may occasionally become intense, either spontaneously or following exposure to sun. In some patients the complaint may be severe enough to interfere with sleep. In rare examples scratch marks may be found. Petges² stressed the high incidence of pruritus in poikilodermatomyositis, a disease which in my opinion represents a variant of ordinary dermatomyositis. This symptom has no genuine differential diagnostic weight, for it may also occur in systemic lupus erythematosus.

(a) *Eyelids* The appearances exhibited by the eyelids are of capital importance, for in the average example of dermatomyositis these parts are often the first to be affected, frequently as a solitary cutaneous sign. As a rule the lids, especially the upper ones, are swollen and colored a rose pink. Careful inspection reveals that the rosy hue is caused by the presence of numerous closely set telangiectases. The edematous infiltration of these parts is generally of the loose type, and the lower eyelids often hang in folds. In other instances, either early or later in the course, there is a firm edema, and sometimes this is spoken of as lardaceous. Occasionally the tissues pit on pressure, sometimes they are tender to touch. The observation of this inflammatory type of edema has occasionally led some observers to suspect the

possibility of dermatitis venenata, for example, occupational dermatitis, poison ivy, etc

The edematous lids may recall the appearance in glomerulo-nephritis, but this belief is usually dispelled by the collateral evidence of abundant telangiectases and by the absence of renal damage of a severe type in dermatomyositis, except in rare instances. The association of swollen eyelids and muscle pains produces a striking similarity to trichinosis, hence the old name pseudo-trichinosis, but, again, the collateral evidence of an inflammatory reaction in the lids (erythema, telangiectasia, pigmentation) provides the differential feature. I have not seen, thus far, the occurrence of subconjunctival hemorrhages in dermatomyositis, a phenomenon more apt to occur in trichinosis, occasionally in glomerulonephritis in the period of azotemia. The other features of trichinosis need not be discussed, but it must be stressed that the differential diagnosis between this disease and dermatomyositis presents difficulties only in the early acute stage. Chronic dermatomyositis shows a vastly different clinical picture. When there is intense edema of the lids with relatively little or unrecognized telangiectasia, angioneurotic edema may be simulated, but the latter is generally more transitory, lacks the evidence of local inflammatory reaction and shows no systemic manifestations of a similar nature, aside from occasional abdominal pain owing to an entirely different cause. In some instances of dermatomyositis it may be essential to spread the lids apart with the object of rendering the skin taut, before telangiectasia in small patches is discovered, for the latter may be obscured by the overhanging folds. In occasional cases of sinusitis edematous areas may be found near the eyes, but close examination shows that the maximum intensity of this process lies close to or at the root of the nose, with lesser involvement as the eyelids are approached. Twice I have encountered such examples of sinusitis accompanied by myalgic pains, and the resemblances to dermatomyositis were further enhanced by the presence of isolated telangiectatic vessels seen chiefly about the nose. The latter manifestation is not uncommonly encountered in chronic sinusitis, and in some cases there may occur, as a later phenomenon, a pure telangiectatic rosacea showing a violaceous hue, possibly the result of passive congestion in the blood vessels in the nose. The cutaneous manifestations occasionally associated with an ophthalmic vein phlebitis are generally differentiated with ease from those in dermatomyositis. The nearest approach to the eyelid and facial lesions in dermatomyositis I once saw in a woman who had swallowed a fishbone that lodged in a pharyngeal pocket behind one tonsil. In this case the constant gagging caused an erythematous and telangiectatic eruption on the face, eyelids, etc. Finally, milky red eyelids may be seen in persons who have been weeping excessively.

In the later stages the eyelids in dermatomyositis may be sites of a dense or a reticulated form of pigmentation. In the former case this may be so similar to suggest the possibility of a phenolphthalein eruption, whereas in the latter instance the picture of poikiloderma is produced. In the latter case a degree of thickening of the skin of the lids may be

found, simulating neurodermatitis. A few observers have noted the occurrence of interspersed small white areas which they have interpreted as a superficial type of atrophy, but true atrophy in the dermatologic sense (caused by advanced changes in the supporting tissues of the cutis) I have not yet encountered in dermatomyositis affecting this locality. When there are whitish, lentil to bean-sized areas of depigmentation scattered in the patches of pigmentation and when these are associated with enough edema to cause thinning of the epidermis, observers may regard such whitish areas as evidence of atrophy, without specifying precisely what they mean by this term.

Occasionally dilated follicles may be seen in the skin of the lids, and there may be fine white scales, often of the adherent type, which may be regarded as "eczematous." Livonius⁷ observed delicate round and linear, porcelain-colored scars at the angles of the eyelids in an instance of this disease. Finally, these parts may show only telangiectasia in more or less compact patches, but at the most this finding of itself is a directing rather than a diagnostic sign.

The lesions in the eyelids are often not only the earliest cutaneous sign but frequently one of the initial manifestations in dermatomyositis. These alterations are usually more conspicuous than the other lesions on the face, and this disproportionate involvement is one of the striking features in the disease. As an early sign it is more likely to be seen in dermatomyositis than in systemic lupus erythematosus, but occasional apparent exceptions may be encountered, especially when the patient is seen late in the course. As a rule, however, implication of the eyelids in systemic lupus erythematosus is met with as a secondary spread from the main eruption on the "butterfly" area of the face in instances showing especially intense lesions in the flush regions, notably after exposure to sun. In advanced stages the differentiation may be more difficult, and in such circumstances the remainder of the clinical picture (cutaneous and internal medical) must be taken into consideration.

(b) *Remainder of the Face* Facial lesions are commonly observed in dermatomyositis, although less often than involvement of the eyelids. Their chief importance lies in their similarity in many instances to the eruption in systemic lupus erythematosus.

In most cases there are faint delicate rosy plaques on the cheeks near the eyelids and the adjacent areas of the nose, and as in the case of the eyelids, numerous closely set telangiectatic areas are the principal component. In other patients the flush area of the face is affected in a manner resembling closely that seen in systemic lupus erythematosus. Thus, there may be observed a bright erythematous eruption arranged in "butterfly" configuration on the cheeks, whereas the bridge of the nose is often, though not always, spared. When there is a pronounced edematous element, erysipelas is simulated owing to the smooth, more or less tense and shiny appearance of the skin (the so-called pseudo-erysipelas or chronic erysipelas of some authors), but this appearance is likely to be encountered far more often in systemic lupus ery-

thematosus (figure 1) It must be stressed that the occurrence of an erythematous facial eruption in "butterfly" arrangement, even when accompanied by adherent scaling, is by no means pathognomonic of lupus erythematosus For example, I have described such an appearance in a case of parapsoriasis en plaques disséminées terminating in mycosis fungoides⁴ Closely set telangiectasia is more frequently found in dermatomyositis, but, as a differential point from systemic lupus erythematosus, this feature must not be overstressed, as there are exceptions As in the latter affection, scaling when present is likely to be adherent in type This may be seen in any part of the face, especially the dorsum of the nose In the acute phases of the eruptions seen in both diseases, follicular hyperkeratosis with prominence of the follicles is often lacking in the flush area of the face These lesions may be observed more frequently in other areas, especially the forehead in dermatomyositis

Generally the facial eruption in dermatomyositis remains visible for some time, even months or years, with occasional and unpredictable exacerbations in intensity It may become fainter and show a delicate violaceous hue or a heliotrope color, and in the later stages it may be succeeded, though not invariably, by pigmentation The pigmentation may be colored a light or dark brown, may be faint or conspicuous, and may occur as smooth or irregular patches or in a reticulated pattern with an admixture of contrasting small whitish areas, pinhead to lentil in size The latter lesions have been interpreted by some observers as evidence of superficial atrophy but, as stated previously, the precise meaning of the term atrophy is not generally defined The pigmented lesions may remain visible for months or even years, as in a case recently reported by me^{1a} This is the type of eruption that is often diagnosed as poikilodermatomyositis, especially when the pigmentation takes on a variegated pattern with an admixture of telangiectases in cases featured by an insidious development of muscular atrophy

It appears, then, that the occasional example of dermatomyositis showing pronounced involvement of the flush area of the face can be differentiated with difficulty, if at all, from systemic lupus erythematosus on the basis of the facial lesions alone In the acute phases of both diseases genuine atrophy in its restricted sense is generally lacking, and what is occasionally described as atrophy usually turns out to be simple thinning of the epidermis For this reason complete regression of such lesions may occur, without leaving gross residual changes So far as dermatomyositis and the majority of cases of systemic lupus erythematosus are concerned, atrophic discoid patches on the face are relatively uncommon Pinhead to lentil-sized areas of so-called atrophy may be found sometimes in dermatomyositis Where the atrophic patches on the face are larger (coin-sized, discoid), one is likely to be concerned either with the relatively less common type of systemic lupus erythematosus superimposed on the chronic discoid form of the disease or the still more uncommon instances of disseminated atrophic lupus erythematosus accompanied by systemic manifestations An instance of the latter variety has been reported by me^{1b}



FIG 1 (Left) The typical "butterfly" eruption of systemic lupus erythematosus (black arrows), the white arrow points to a swollen gland in the neck, a not uncommon finding in this disease and independent of tuberculosis.
 FIG 2 (Right) The dermatomyositic facies, more pronounced than usual, as exemplified in a case of Fuhs. The arrow points to the swollen parotid gland, erythematous and telangiectatic skin of the eyelids. In the stage of pigmentation the term "poikilodermatomyositis" is generally used by dermatologists (see text).

The forehead and temples are commonly affected in dermatomyositis, and also in systemic lupus erythematosus, although less often. In some cases this region may be the initial site of involvement of the skin in dermatomyositis, and symmetrical pigmented patches are frequently the end-stage of lesions starting primarily as telangiectatic erythematous areas. The occurrence of small patches in the skin directly cephalad to the eyebrows, without pronounced involvement of the eyelids, is encountered more often in systemic lupus erythematosus than in dermatomyositis, but the reverse seems true in the case of patches on the forehead and temples, associated with follicular elevations. On the basis of these points alone it would be hazardous, however, to establish a differential diagnosis.

In dermatomyositis similar telangiectatic erythematous areas may also be seen occasionally on the upper lips, the chin and about the mouth. In some instances a perioral pallor is present, and this cannot always be correlated with the degree of secondary anemia.

No detailed description of the evolution of the lesions on the face has been given, for it is essentially the same as in the case of the eyelids.

THE DERMATOMYOSITIC FACIES

This is composed of two elements: (1) definitely swollen eyelids with narrowing of either one or both lid spaces together with a degree of edematous involvement of the adjacent portions of the cheeks and nose, (2) a background of faint rosy or pale blue colored skin (by some described as wine-colored). The net effect of these appearances is to create a sort of heliotropic bloating of the face, resembling the early stages of cadaveric decomposition. This type of facies is often seen and is easily recognized (figure 2).

In some instances it may be modified or obscured by accessory phenomena occurring in the subcutaneous and muscular tissues of the face.

(c) *Scalp* Alopecia, total or incomplete, may occur in dermatomyositis. Often this seems to be related to the severity of the illness, especially the height of the fever, but this is variable, and there is nothing specific in this phenomenon. Causade and Aleshkowska⁷ observed a cyanosed appearance of the skin of the scalp in association with total alopecia of this part. The hair may regrow with subsidence of the illness.

Commonly there occurs more or less diffuse redness or a violaceous erythema of the skin of the scalp, with telangiectasia, more or less scaling of a branny type, and preservation of the hair. Although these lesions may suggest the possibility of dermatomyositis, they are not distinctive, for similar manifestations may be seen in other diseases, including systemic lupus erythematosus. However, in cases of discoid lupus erythematosus with superimposed systemic lupus erythematosus, it is not rare to encounter genuine discoid lupus patches in the scalp, and their occurrence, which I have observed in at least half a dozen instances, favors definitely the diagnosis of

lupus erythematosus Such patches of coin-sized discoid atrophy I have not yet seen in any authentic example of dermatomyositis

(d) *Ears* In dermatomyositis the ears, especially along the rims, are often sites of erythematous areas generally the size of a pea or larger, and sometimes there is coalescence with formation of extensive patches Here, too, telangiectasia is an important component of the lesions Thickening and swelling of the lobes of the ears may be observed sometimes It is not uncommon to find small areas of telangiectasia distributed irregularly along the rims The erythematous lesions are frequently covered by adherent scales Dilated follicular openings⁷ and pigmented spots may be seen occasionally Of greater interest is the occurrence of atrophic areas that often appear to be indistinguishable from those in systemic *lupus erythematosus*, except that as a rule these lesions are smaller and more discrete in dermatomyositis Only in uncommon instances is there extensive atrophy of the ears, and rarely this may be of a character to permit the subjacent veins to shine through Rare, also, is the occurrence of subcutaneous hemorrhages in these parts⁸ In occasional instances the area of skin behind the ears or in the retro-mandibular regions may be the earliest sites of eruption, with spread to contiguous or remote parts of the body Exceptionally, small ulcerations may be found in the external auditory canal, which may be painful and recurrent¹⁰

It appears, then, that the differentiation of dermatomyositis from systemic *lupus erythematosus* on the basis of these appearances is difficult, if not impossible

(e) *Neck, Chest and Abdomen* These parts are often implicated in dermatomyositis The cutaneous changes are of two types which may occur independently or combined, and there are also transitions These appearances may be modified, especially by edematous infiltrations involving the skin, subcutaneous tissues and muscles

1 There are smaller and larger patches, discrete or coalescent, showing attributes similar to those already described in the early stages, erythema of varying grades, telangiectasia and some scaling, usually of the fine adherent type, in the later stages, pigmentation in solid or reticulated pattern, with telangiectasia and interspersed whitish areas of irregular size and distribution, creating an appearance for which the term *poikilodermatomyositis* is often used Occasionally the follicles may be seen as flat, raised, tiny, firm whitish or brownish elevations With more pronounced edema, the affected areas are often tense, smooth, shiny and atrophic in the sense of a thin epidermis

The V-shaped area of the neck is frequently involved in dermatomyositis, generally in the form of irregular pale red or faintly violaceous patches showing indefinite margins In some of these cases, at least, the influence of exposure to sun seems manifest This part of the body is affected more frequently in systemic *lupus erythematosus* in which its occurrence is the rule (figure 3) In systemic *lupus erythematosus* the outline of this lesion is often fairly circumscribed and more apt to conform to the portion of the neck left free by the dress (women) and to the exposed portion of the

bathing-suit, whereas the areas covered by the shoulder straps are generally spared. Instances exhibiting lesions with indefinite margins that fade gradually into normal skin are, however, also encountered in systemic lupus erythematosus, but this is the rule in dermatomyositis. In some cases of systemic lupus erythematosus the V-shaped area of the neck is the site of an



FIG. 3. Systemic lupus erythematosus in a young girl. Note involvement of the exposed areas (A) and the areas covered by the shoulder straps (B). The black arrow points to a lesion on the right forearm, the white arrow points to a lesion on the left forearm.

eruption that progresses to form either a shiny, smooth, genuinely atrophic solid patch or many similar interspersed lesions. Such solid plaques of atrophy definitely favor the diagnosis of systemic lupus erythematosus as against dermatomyositis.

On the other hand, the posterior aspect of the neck is far more often involved in dermatomyositis. The occurrence of diffuse pigmented patches in the nuchal region with spread to the lateral portions of the neck is, perhaps, in some ways distinctive of dermatomyositis, and not rarely may be the initial site of the eruption. Cutaneous lesions behind the ears, in solitary and discrete areas, are seen in both systemic lupus erythematosus and dermatomyositis.

In some instances of dermatomyositis the resemblances to pellagra seem considerable because of the pigmentation of the neck (vaguely resembling Casal's collar), pigmentation of the face, alterations in the oral mucous membranes, patches on the dorsa of the hands (which are, however, vastly different in appearance), etc. On several occasions I have encountered instances in which the diagnosis of pellagra or of riboflavin deficiency or some such avitaminosis had been entertained, and it seems to me that the pendulum of vitamin B deficiency needs considerable steadying. Dermatomyositis, it may be noted, is also a disease in which exposure to sun often exerts an influence on the eruption and its localization.

The pigmentation in dermatomyositis may be so intense and widespread as to simulate Addison's disease. The finding of a low blood-sodium is not adequate to determine the differential diagnosis.

2 Less frequently there are encountered, chiefly on the anterior and posterior aspects of the chest, but also on the neck, abdomen and other parts, small areas of atrophy¹¹ similar to those to be described in connection with the skin overlying the articulations. These lesions, pinhead to a pea or larger, are often the clinical counterpart of what dermatologists call "white spot disease" or the "visiting card" type of scleroderma. However, the differentiation of the atrophic lesions in dermatomyositis from "white spot disease" (a heterogeneous group of cutaneous anomalies) is not difficult in view of the associated features in the skin and the distinctive systemic manifestations. These appearances in dermatomyositis are of interest in showing that this type of atrophy (involving the supporting tissues in the upper cutis as well as thinning of the epidermis) is not pathognomonic per se of a single disease but must be evaluated on the basis of the entire clinical picture. Such small areas of atrophy, occasionally grouped, are more often seen in dermatomyositis than in systemic lupus erythematosus, and their relatively common occurrence on covered portions of the body seems noteworthy.

The cutaneous alterations in dermatomyositis, especially those on the trunk, have been compared by some observers with radiodermatitis, but in reality the resemblances are superficial. In dermatomyositis the involved areas are as a rule larger, often covering extensive tracts of skin, the telangiectasia is finer, more closely set and more regularly arranged, the peculiar

sclerosis of true skin as found in radiodermatitis is absent, although it may be simulated in advanced stages of dermatomyositis, particularly when the underlying muscular and subcutaneous tissues have undergone atrophy, the painful ulcerations of radiodermatitis never occur, although occasionally in dermatomyositis there may be ulcerations arising from a variety of causes to be mentioned later, there is no history of the use of roentgen-ray, radium or ointments containing radioactive substances (if there is such a history, the lesions extend far beyond the point of application of these therapeutic agents), and, finally, the clinical picture as a whole, both cutaneous and systemic, is vastly different in these two affections

f The Limbs (1) Eruption over the articulations To discuss these lesions as a unit is not arbitrary, for in most cases of dermatomyositis the skin overlying the joints is affected characteristically, whereas the intervening portions of the limbs are spared. Indeed, a few observers have stressed this localization about these so-called pressure points. Study of this aspect of the eruption provides data substantiating the view that dermatomyositis pursues a variable course ranging from the mild cases to the acute, subacute and chronic forms with their transitions into the clinical pictures of myositis fibrosa, myositis ossificans, etc. These observations, moreover, shed more light on the concept of this disease and, especially, the prognosis

For convenience this group of lesions may be discussed under the following two headings (A) those related to the small joints, particularly of the fingers, (B) those related to the larger articulations

(A) The lesions found in the skin overlying the small joints of the hands in dermatomyositis represent an outstanding feature of this disease in all its stages. In many cases they appear as the initial manifestations. By themselves these alterations are highly characteristic and take on the attributes of a pathognomonic appearance, notably when correlated with the remainder of the clinical picture. In obscure cases these lesions may constitute a "revealing" sign. Without in any way detracting from the importance assigned to them by Gottron,¹⁶ it will be seen later that other diseases are accompanied by somewhat similar manifestations, but, as a rule, their differentiation is not difficult.

In the early stages these lesions appear in the form of ill-defined, somewhat edematous, blotchy red telangiectatic patches situated over the metacarpophalangeal and interphalangeal joints. In some cases only a few of these articular regions are affected, but generally the eruption is bilateral and often symmetrical. The cutaneous lesions over the metacarpophalangeal joints are observed more often and in more characteristic form than those in relation to the interphalangeal joints, although both are frequently affected together. Sometimes also, the plaques are fairly well outlined. In most cases the lesions are dull red, violaceous, or have a cyanosed hue, but as in the case of the typical telangiectasia commonly forms the major component. It is noteworthy that these localities are sites of terminal circulation, and that the eruption is often a lead upon the state of the circulation in these

areas. The ectatic vessels, when less numerous, are easily overlooked, as, for example, in the case of Mihañ and Rimé¹² in which no mention was made of them until their presence was pointed out as a curious feature by Lortat-Jacob¹³ in his discussion of that case. On a number of occasions I have also seen these lesions overlooked. Most often there is seen a fine adherent type of scaling, and undoubtedly it is this feature that has caused a few observers to speak of a dry dermatitis¹⁴. In occasional examples I have encountered gradually increasing pigmentation over the knuckles, without a preceding telangiectatic or erythematous eruption, so far as I could tell. Such pigmented patches, generally ill-defined in their contours, may be seen sometimes in other affections, such as ordinary rheumatoid arthritis, and cannot be regarded, therefore, as bearing special significance. Pick¹⁵ described the occurrence of necrotic hemorrhagic areas in the skin overlying the phalangeal joints of one hand. Warszewski and Radzinski¹⁶ recorded the presence of peculiar vesicular lesions over the metacarpo-phalangeal joints. Incisions of the vesicles yielded a small amount of thin, apparently nonpurulent fluid. The phenomena observed in these two cases represent examples of a more intense exudative process such as is rarely encountered in this situation in dermatomyositis, but such lesions are met with occasionally in this disease in other parts of the body, usually as isolated manifestations.

When circumscribed plaques are formed, they appear as bluish-red areas with a fringe of telangiectatic vessels, often associated with dilated capillaries that course over the central portions of the lesions. This appearance may be retained for weeks or months, may disappear, or may go on to assume any one of the following characteristic aspects:

a The lesions may consist of a mosaic of papules in close apposition to one another, so that the normal lines of skin seem exaggerated (figure 4). There may or may not be a degree of atrophy, but, according to my clinical observations, this would be restricted to simple stretching of the epidermis. The pseudo-lichenification in these generally nonpruritic plaques has often been confounded with neurodermatitis, according to my observations, but on the other hand, the bluish color may remind the observer of lichen planus. This mosaic appearance is common and is often attended with more or less scaling of an adherent type.

b The lesions may be sites of "soft" atrophy (figure 5) similar to that seen in *acrodermatitis chronica atrophicans*, occasionally *epidermolysis bullosa dystrophica*. Although this appearance may be best witnessed in the skin about the larger articulations, it is also encountered in characteristic form over the small joints. The skin is thin, wrinkled, shiny, slightly scaly and often colored bluish-red with a superimposed livid hue.

c In other cases there are observed whitish plaques resembling porcelain or alabaster, with some depression of the central portions and a surrounding zone of telangiectasia. These vary in size from that of a pea to an area covering the entire knuckle, especially over the metacarpo-phalangeal joints.

Owing to the anatomical relations of the knuckles, these atrophic lesions are apt to create the impression of pronounced infiltration, and, from their appearance and feel, may be regarded as an example of "hard" atrophy. This effect is enhanced by the hyperkeratosis (scaling) commonly encountered in these areas. In some instances these changes are so pronounced that the lesions seem to be adherent to the underlying bone, without in any way resembling scleroderma.

(B) Similar changes may be found in the skin about the larger joints, such as the elbows (figure 6), knees, ankles, wrists, etc. In my observations the elbows were the most frequent sites and were nearly always associated with involvement of the knuckle areas. Dowling¹⁷ recorded an instance in which the initial manifestations appeared about the elbows, only to disappear later. Most commonly there are observed reddish-blue or dull red flat patches showing a striking telangiectatic element and adherent scales. When scaling is pronounced, psoriasis may be simulated vaguely, as, for example, in Semon's case.¹⁸ In later stages the skin takes on attributes resembling those seen in acrodermatitis chronica atrophicans or healed epidermolysis bullosa dystrophica, and becomes thinned out, wrinkled, and like cigarette-paper. According to my own observations, this "soft" type of atrophy is especially common. I have not yet had the opportunity of seeing the alabaster-like, whitish, "hard" atrophic patches in areas of skin about the larger articulations, such as is seen so often over the knuckles. However, Schuermann^{11b} observed porcelain-like spots over the malleoli and patellas. Bamber¹⁹ saw whitish depigmented macules over the wrist, associated with telangiectasia, but he was not certain that these spots were actually atrophic. I have seen the skin over the knees discolored a deep reddish-blue, such as may be commonly found in patients with chronic cardiac failure, and once I encountered a telangiectatic eruption about the ankles, the telangiectases being arranged in circular formations with simulation of Majocchi's disease (purpura annularis telangiectodes). The knees may be sites of pigmented patches with a surrounding zone of telangiectasia.²¹

Since much clinical significance has been assigned to the eruption about the articular areas, especially the small joints of the hands, it seems desirable to discuss, according to my own observations, some of the many diseases that may be accompanied by similar manifestations.

a. Systemic Lupus Erythematosus. In this affection the cutaneous areas about the articulations are sometimes affected, but on a comparative basis such changes are encountered far more often in dermatomyositis. A few instances of systemic lupus erythematosus with knuckle lesions have been

FIGURE 6. A case of dermatomyositis in a child. The "raccoon" lesions on the elbows and knees, and telangiectases about the knuckles with calcareous deposits (figure 6a). A second dermatomyositis in a patient with the "raccoon" lesions on the elbows and knees, and telangiectases about the knuckles with calcareous deposits (figure 6b). The calcareous deposits are the same patient (figure 6c). The calcareous deposits are the same patient (figure 6d). The calcareous deposits are the same patient (figure 6e). The calcareous deposits are the same patient (figure 6f). The calcareous deposits are the same patient (figure 6g). The calcareous deposits are the same patient (figure 6h). The calcareous deposits are the same patient (figure 6i). The calcareous deposits are the same patient (figure 6j). The calcareous deposits are the same patient (figure 6k). The calcareous deposits are the same patient (figure 6l). The calcareous deposits are the same patient (figure 6m). The calcareous deposits are the same patient (figure 6n). The calcareous deposits are the same patient (figure 6o). The calcareous deposits are the same patient (figure 6p). The calcareous deposits are the same patient (figure 6q). The calcareous deposits are the same patient (figure 6r). The calcareous deposits are the same patient (figure 6s). The calcareous deposits are the same patient (figure 6t). The calcareous deposits are the same patient (figure 6u). The calcareous deposits are the same patient (figure 6v). The calcareous deposits are the same patient (figure 6w). The calcareous deposits are the same patient (figure 6x). The calcareous deposits are the same patient (figure 6y). The calcareous deposits are the same patient (figure 6z).

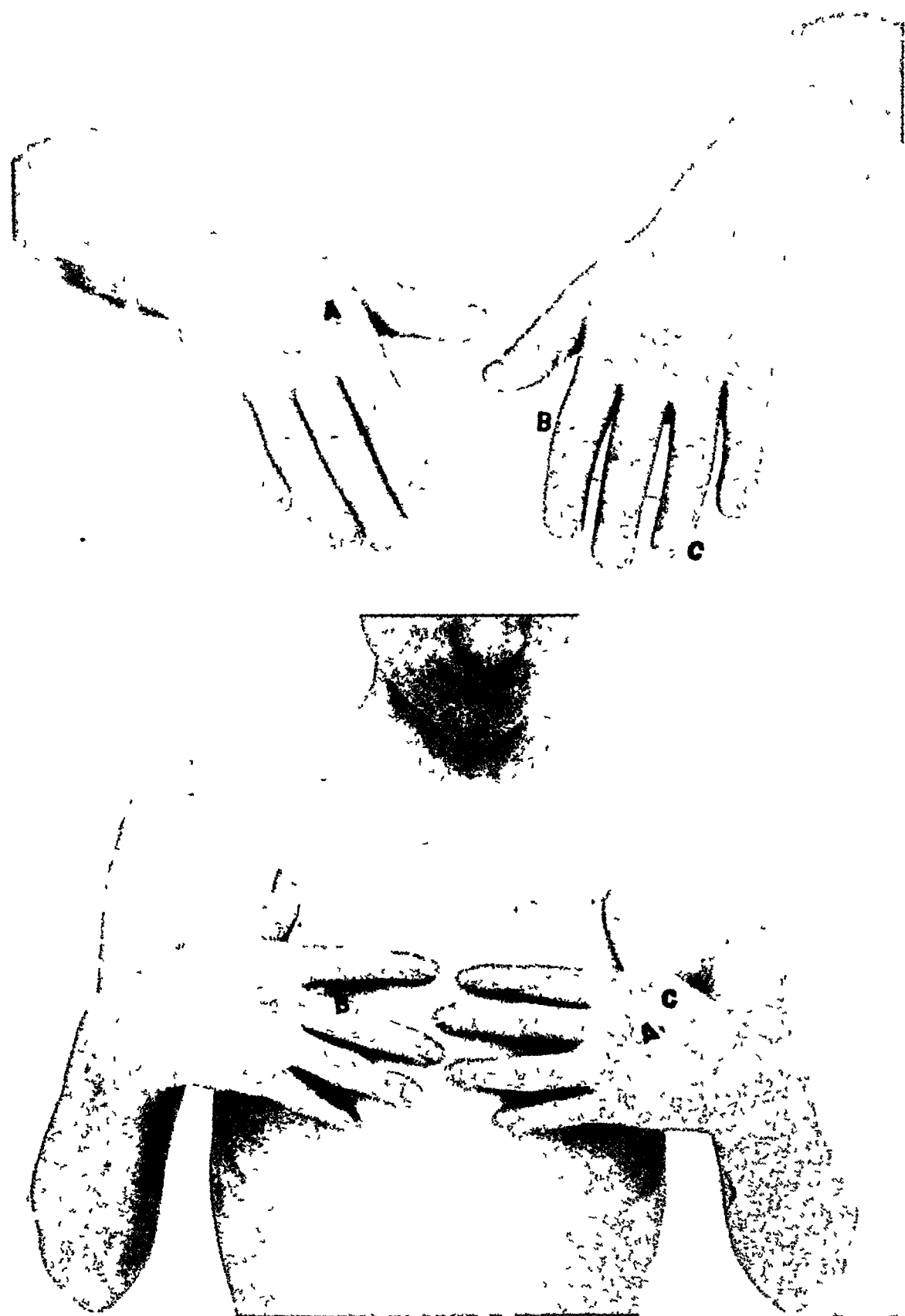


FIG 4 and FIG 5

recorded, but where adequate clinical details are available, as in Klingmüller's case, it appears that the condition was in reality dermatomyositis. It must be admitted, however, that the differentiation in such instances may be difficult at times, if not impossible at certain stages. I have encountered at least



FIGURE 5. The same patient shown in figure 3. Note the atrophic lesions about the elbows and the face, resembling scleroderma, and the telangiectasia. The white arrow points to the perioral area showing telangiectasia. (From Keil, H. *Arch. Int. Med.*, 1931)

The patient's skin shows whitish depressed atrophic patches with peripheral telangiectasia. The telangiectasia and telangiectasia occurred irregularly over the face and neck, but it is interesting to note that these lesions were distributed in a symmetrical pattern between the small joints. Although, therefore, the

knuckle lesions in dermatomyositis are not pathognomonic per se, their occurrence provides, at the very least, a significant "revealing" sign, and their importance becomes enhanced when they are evaluated in terms of the other features in this disease. In some instances, and these are becoming fewer in number, the differential diagnosis between dermatomyositis and systemic lupus erythematosus will rest on the composite clinical picture and the subsequent course.¹

b. Acrodermatitis Chronica Atrophicans The lesions about the articulations in dermatomyositis, especially the larger joints, exhibit considerable resemblance to acrodermatitis chronica atrophicans (figure 6). This is particularly true of the early stages of the latter disease, when the eruptive elements are more or less confined to the immediate neighborhood of the large joints, such as the elbows. However, in the later stages a number of differences are found: (1) in acrodermatitis chronica atrophicans the skin becomes so thin as to permit the subjacent veins to shine through, but such a degree of atrophy is uncommon in dermatomyositis, (2) in acrodermatitis chronica atrophicans there is spread to involve large tracts of skin with the "soft" type of atrophy characteristic of this disease, but such extension of atrophy of this type I have not encountered in dermatomyositis, nor do I know of its occurrence in any recorded case, (3) in acrodermatitis chronica atrophicans it is common to encounter linear sclerotic-like bands along the ulnar bones, etc., which seem not to occur in dermatomyositis, (4) the systemic features and the other clinical manifestations are vastly different in these diseases.

c. Epidermolysis Bullosa Dystrophica In the healing or healed stage of epidermolysis bullosa dystrophica the skin about the knuckles and the larger joints may be sites of lesions that are the counterpart of the cigarette-paper-like atrophic patches in dermatomyositis. The former affection is distinguished by the frequent onset at birth or shortly after, the familial history, the commencement with bullae, the frequent concomitance with dystrophic changes in the nails, the oral manifestations that are often frankly bullous, rarely the conjunctival alterations in the nature of "essential shrinkage," etc. The general symptoms of dermatomyositis, including the muscular phenomena and the other cutaneous changes, especially in the face, are absent in epidermolysis bullosa.

d. Chronic Cardiac Failure In chronic cardiac failure, particularly that associated with rheumatic heart disease, involvement of the skin overlying the knuckles, elbows, knees, etc., occurs sometimes. These lesions appear as superficial patches colored reddish, reddish-blue or purple red (local cyanosis), accompanied occasionally by hyperkeratosis (scaling) of variable degree. The latter may attain an enormous degree of development in some instances.²⁰ Generally these areas are colder to the touch than the neighboring parts, and it must be stressed again that they represent points of terminal circulation. These lesions are probably analogous to the so-called "mitral flush or facies" observed in long-standing examples of mitral stenosis, and to chronic passive

congestion of the viscera seen in postmortem examinations in such instances. Commonly there are associated follicular-papular lesions on the legs and forearms, similar to those seen in chilblains and in women with "poor circulation." In addition, it is relatively common to find reddish brown papules, often with scratched tops, sometimes more or less grouped (usually less) about the articulations, and generally healing with the formation of centrally depressed scars enclosed by a peripheral narrow ring of pigmentation. In the healing or healed stages papulonecrotic tuberculides are simulated, but in my view these manifestations have an entirely different significance from the somewhat clinically similar tuberculides found especially in children suffering from active lymph node tuberculosis with generalization of the infection (secondary stage of Ranke).

The lesions about the articulations may, therefore, more or less resemble those in dermatomyositis, but in chronic cardiac failure they represent part of an entirely different clinical picture.

c Rheumatic Subcutaneous Nodules In occasional instances, of which I have seen one striking example, the presence of rheumatic subcutaneous nodules in the tendons passing over the metacarpo-phalangeal joints may cause redness of the overlying skin. Generally only a few knuckles are affected irregularly. This appearance is probably caused by local pressure on the superficial skin over the joints, for, as the subcutaneous nodules diminish in size, the redness disappears. Scaling seems not to occur. At least it was not present in the case under my observation.²¹

f Angiokratoma of Mibelli This condition affects the skin over the bony protuberances of the limbs, especially the hands and feet, sometimes the knees and elbows. When situated over the knuckles, the lesions may simulate closely those found in dermatomyositis. As a rule the eruption is composed of discrete, isolated, rough, hard and warty bluish papules, pinpoint to pin-head in size. Diascopic examination shows dark red puncta corresponding to enormously dilated capillaries or actual hemorrhagic extravasation, and pricking with a needle is likely to lead to free bleeding. In addition to the above localizations, the lesions are often scattered irregularly over the fingers, toes and dorsa of the feet. This affection occurs in young adults of both sexes, generally has its onset at an early age in persons, especially girls, with a previous history of chilblains or pernio, and is occasionally seen in association with lupus erythematosus. The morphology of these lesions as well as the general clinical picture distinguish this disease from dermatomyositis.

g Kaposi's Idiopathic Hemorrhagic Sarcomatosis In some instances of this disease the eruption shows a definite predilection for the skin situated over the small joints of the hands as well as the large articulations. In the average case this affection is easily differentiated by the occurrence of peculiar reddish brown or reddish blue plaques near the terminal parts of the digits, the presence of nodules, the fairly distinctive color of the lesions, the characteristic changes in the lower limbs with the keratotic areas over the toe and the frequently associated "elephantiasis" of the leg, the special tendency to

the supervention of sarcomatous changes, the entirely different clinical course with involvement of lymph nodes, spleen, gastrointestinal tract, etc. It must be stressed that (a) this disease may also occur in children in whom it is perhaps a little more difficult to recognize, (b) a part of the cases originally classified as erythema elevatum diutinum (q.v.) represented in reality examples of Kaposi's hemorrhagic sarcomatosis.

h Erythema Elevatum Diutinum In typical cases of this affection there are observed bluish red, circumscribed, flat, button-like, infiltrated, more or less persistent plaques situated over the joints especially the small articulations of the hands and larger joints, such as the elbows, knees and ankles. In their further evolution these lesions disappear, often leaving pigmented spots as sequelae.

Study of cases formerly included in this category indicates the heterogeneity of the group²¹. Thus, examples of subcutaneous nodules in rheumatoid arthritis, Kaposi's sarcomatosis, granuloma annulare and probably other affections have been included in older reports. Weidman and Besancon²² made an outstanding effort to establish this entity on clinico-pathologic grounds, but in my view the nosologic status of this disease is still far from clear. Above all, it cannot be accepted that this eruption, assuming that the two cases described by Weidman and Besancon were of the same nature, represents a "rheumatic" dermatosis, unless one wishes to employ this name in a vague sense. It is interesting that rheumatic fever is one of the common diagnoses for cases that eventually turn out to be dermatomyositis. I have recorded^{1a} two such instances, and a critical review of other similar cases indicates clearly that the initial impression of rheumatic fever could not be substantiated post mortem. Weidman and Besancon described certain anatomical findings as characteristic, perhaps pathognomonic, of erythema elevatum diutinum, but complete acceptance of this view awaits study of a larger casuistic material. The illustration of the eruption on the hands in their second patient²³ is a replica of what I have described in dermatomyositis, figure 4 in this article may be compared with their figure 10.

Once I encountered an unusual instance showing similarities to erythema elevatum diutinum. Early in the course there were resemblances to erythema multiforme exsudativum and lupus erythematosus owing to the presence of lesions over the small joints of the hands, the ears and face. This was probably an example of extracellular cholesterosis. In a case recently reported by Gately and Ketron²⁴ as one of erythema elevatum diutinum, it is interesting that Urbach mentioned the possibility of extracellular cholesterosis in the discussion of this case. The resemblance between these two diseases is enhanced further by the occurrence of joint pains in both, or at least pains that have been interpreted as being of articular origin²⁵.

i Miscellaneous Affections Many other conditions are sometimes accompanied by alterations in relation to the knuckles, for example, xanthoma tuberosum multiplex, xanthoma diabeticorum, gout, psoriasis, neuroder-

matitis, certain congenital anomalies, Raynaud's disease, scleroderma, etc. It is not difficult, as a rule, to differentiate the various manifestations of the aforementioned diseases from the appearances in dermatomyositis.

2 *Remainder of Limbs* (a) Proximal portions (arms, forearms, thighs and legs) The areas of limb between the joints are generally spared, with certain exceptions to be mentioned later in discussing the skin-muscle relationship. The continuity of skin over the limbs is more apt to become involved when the exanthem takes on a widespread distribution, and in such cases the extensor aspects of the limbs are usually favored. However, the flexor aspects (flexures of elbows and knees, etc.) may show edema and fissuring. In Towle's case²⁶ the skin became so tense that it broke at the bend of the elbow and the inner aspect of both thighs, resulting in hernial protrusions of the subcutaneous fat²⁷ but such a phenomenon belongs to the rarities. The eruption on the limbs is the counterpart of the lesions previously described. In instances featured by a universal distribution and pronounced scaling, the picture of an exfoliative dermatitis may be produced.²⁸

(b) Distal portions (hands and feet) Under this heading a few interesting manifestations remain to be mentioned, among them certain "vasomotor" phenomena.

1 In addition to the characteristic knuckle lesions, there are commonly associated with them telangiectatic and scaling small areas colored red to reddish blue and situated between the distal interphalangeal joints and the proximal nail folds, with encroachment on the latter structures (figure 4). These appearances are often duplicated in systemic lupus erythematosus (figure 3) and probably other diseases, hence they are distinctive in only a limited degree. I have seen cases labeled as systemic lupus erythematosus on the basis of these lesions in obvious examples of dermatomyositis.

In a number of recorded cases the eruption on the hands has been diagnosed originally as occupational dermatitis, so that this disease sometimes has medicolegal implications. I have recorded two such examples and reviewed the factor of lead in its possible relation to the onset and accentuation of dermatomyositis.¹ Hendry and Anderson²⁹ reported the case of a photographer's assistant in whom a positive patch test to hydroquinone was obtained, but the significance of this finding was impaired because of the patient's improvement despite continuation at work.

2 The fingers and toes, especially the former, are often sites of phenomena generally classed as vasomotor in origin. These include paresthesias (numbness, tingling, etc.) and acrocyanosis of various grades with transient or permanent clinical picture resembling Raynaud's disease. In a group of 10 cases of dermatomyositis O'Leary and Warsman³⁰ recorded the occurrence of paresthesias in nine patients and acrocyanosis or variants of this state in three. They noted that the paresthesias were neither pronounced nor prolonged. It seems to be true of the phenomena classed as acrocyanosis that they are to be regarded as relative rarities in these cases; the term

pseudo-Raynaud's syndrome is used. As a rule, the attacks, which may appear either as an initial manifestation or as an intercurrent event, are limited to the first stage of local syncope (fingers white and "dead"), occasionally the second stage of asphyxia (blue fingers), but rarely the final phase of gangrene. These attacks occur generally in the winter. In Ingram and Stewart's patient mild episodes of acrocyanosis appeared during each of the three winters preceding the onset of dermatomyositis.³¹ Bailey³² reported an instance in which there was a previous history of chilblains at an early age. I¹⁶ described the case of a young man who had several such attacks intercurrently, and it may be noted that a relatively high percentage of such patients were men.

In another publication¹⁶ the point has been stressed that a pseudo-Raynaud picture may be encountered in a number of affections, such as dermatomyositis, systemic lupus erythematosus, scleroderma, etc. Some observers have attempted to ally these diseases on the basis of these vasomotor manifestations, but this view is hazardous. Whether similarity in pathogenesis necessarily means identity in etiology seems doubtful, and this fundamental problem still remains to be clarified.

From time to time observers have also attempted to establish an absolute relation between scleroderma and dermatomyositis. This hypothesis, based chiefly on analogy, may be regarded as lacking in proof. On this point my views are in complete accord with those set forth recently by O'Leary and Waisman³⁰ who also sharply differentiate these diseases.

3 There came under my observation a probable example of systemic lupus erythematosus, the only one I have seen with undoubted involvement of the large muscular groups, in which the ventral surfaces of the distal ends of all the fingers were sites of a deep red, sharply circumscribed eruption. These lesions occupied about an inch of the surface and extended toward the free margins of the nails on the dorsal aspects. The appearance simulated somewhat that seen in psoriasis. This case is mentioned as a curiosity in view of the definite muscular involvement in a case in which the findings at necropsy were consistent with the diagnosis of systemic lupus erythematosus. However, as I saw the patient on but one occasion and had no real opportunity to study the clinical course, it seems wise to suspend judgment until more examples of this type are observed.

Schatzki³³ described an instance of dermatomyositis in which the large toes were sites of a few scattered erythematous painless lesions. Such spots are not to be confounded with the Osler nodes.²¹

4 Palms and Soles. Involvement of the palms and soles is uncommon in dermatomyositis. In this respect there is a definite contrast between this disease and systemic lupus erythematosus, for in the latter affection these areas, especially the palms, are frequent sites of red or reddish blue, discrete and coalescent spots (figures 3 and 7). A few observers have recorded examples of dermatomyositis that are exceptions to the above rule. Thus, Crevald³⁴ saw large red spots on various parts of the palms. Pick¹⁵ de-

scribed a case in which he observed, in the terminal stage, lentil-sized, bluish-violet, non-circumscribed painless spots in the palms. Such lesions may more or less resemble Janeway spots,²¹ and it may be noted that in this case the postmortem examination revealed no evidence of acute bacterial endocarditis. Dohi²⁵ recorded the occurrence of many telangiectases in the palms and soles, with the epidermis being apparently thinner than normal. In one of my cases there had been a punctate type of keratoderma.^{1a} Wolf and Wilens (case 1)²⁶ described an example of dermatomyositis in which the onset occurred with a "dermatitis" of the palms. These are all exceptional observations. Involvement of the palms and soles, especially the former, speaks definitely for systemic lupus erythematosus as against dermatomyositis.

Petges and Petges,² discussing poikilodermatomyositis, also stressed the rarity of such lesions in this disease. In my view^{1b} this syndrome is merely a morphologic variant of ordinary dermatomyositis.

5 Nails. Involvement of the structures about the nails is but rarely mentioned in accounts of dermatomyositis, yet such changes are often seen (figures 5 and 8). The occurrence of erythematous and telangiectatic lesions in the soft parts about the nails is fairly common, and, as a rule, they may be found along the rims of both the proximal and lateral nail folds. As stated, similar changes are encountered in systemic lupus erythematosus and probably other diseases. Of greater diagnostic significance is the appearance of hyperkeratotic alterations involving chiefly the proximal nail fold, occasionally portions of the lateral nail folds. These are recognized as yellowish tissue that projects irregularly or unevenly for a short distance over the lunula. Sometimes the changes are slight, but within the past few months I have seen three instances exhibiting these lesions in pronounced form. All of these cases were associated with alterations in the skin about the knuckles and the soft parts immediately surrounding the nail folds. In one instance there were also subungual hyperkeratotic accumulations underneath the lateral margins of the thumb nails, but such changes are much less important. It is my belief that hyperkeratosis involving the proximal nail folds is analogous to the whitish leukoplakia-like patches found in the oral mucous membranes (q.v.). It appears that anatomical peculiarities may explain the yellowish color of the former and the whitish appearance of the latter. Occasionally similar lesions are seen in the toes (figure 8). In some instances^{17, 18} these alterations are covered partly by crusted areas which on removal reveal superficial defects. The changes in the nail folds may undergo complete involution.

On the other hand, the nail plates are practically always spared. At least the changes are neither pronounced nor distinctive. Ingram and Stewart recorded an apparent exception, a patient who had dystrophic nails. The description of the changes (brittle nails) indicates that there was no connection with the severity of the alterations observed, for example, in dermatomyositis. Moreover, it seems possible that in their case the changes were related to the Raynaud-like attacks in the fingers. I have



Fig 7 (*Left*) A case of systemic lupus erythematosus in a child. The erythematous, telangiectatic and slightly hemorrhagic lesions in the palms and ventral aspects of the fingers (*A* and *B*).

Fig 8 (*Right*) From the same patient as in figure 4 (after Engelhardt). To illustrate the lesion in the proximal nail fold of the large toe.

not seen massive hemorrhage into the nail beds as may occasionally occur in systemic lupus erythematosus ⁶

The incidence of the hyperkeratotic lesions about the proximal nail-folds is probably fairly high. These changes are often overlooked because they are not conspicuous. Occasionally they may appear as one of the early signs of dermatomyositis ³⁷. It is difficult to state at present whether these manifestations are distinctive. Although I have, thus far, not met with them in systemic lupus erythematosus, a recent case of diffuse progressive scleroderma under my observation showed similar lesions.

g Miscellaneous Areas of Skin The buttocks and sacral regions are occasionally affected, rarely the scrotum. The evolution of the lesions is analogous to that already described, and in these situations the eruptions lack specific attributes. Involvement of the buttocks by telangiectatic and superficially atrophic patches may only vaguely simulate the characteristic changes in acrodermatitis chronica atrophicans.

MUCOUS MEMBRANES

The term dermatomyositis, first introduced by Oppenheim to designate the oral manifestations, is now considered superfluous, as these appearances are an integral part of the disease. Schuermann ^{11b} collected the records of more than 50 cases showing these lesions, an incidence of about 20 per cent. This is a conservative estimate, for owing to a number of technical difficulties, the mucous membranes are usually studied with less care. Of these parts the mouth and pharynx are most frequently affected, the larynx, conjunctiva and nose less commonly. Schuermann and his pupil, Memmert ¹⁸ have reviewed the subject exhaustively. In the main my observations are in close accord with theirs, although in the account to follow certain differences in the evaluation of the lesions will be discussed.

Before considering the subject, several points need to be mentioned. (a) the morphology of lesions in the mucous membranes is influenced considerably by a variety of anatomical factors ¹⁹, (b) in some diseases there is an inherent tendency toward polymorphism in the enanthem, whereas in other cases this multiformity in appearance is due, in large part, to superimposition of such secondary phenomena as maceration of sputum, etc., (c) although in dermatomyositis various lesions may be observed in the mucous membranes, only an occasional type can be considered as being somewhat distinctive. The remaining appearances are, therefore, best remembered in a negative way. In general, the lesions in the mouth and other parts resemble closely those seen in systemic lupus erythematosus, leukoplakia, lichen planus, occasionally syphilis, etc.

1. Mucous Membrane of the Mouth and Upper Respiratory Tract 1. *Erythema*—This occurs as pinhead to lentil size or larger, flat, bright red patches, on any portion of the oral mucous membrane, and less commonly on the larynx and rarely the nose. In the mouth

there is diffuse involvement of the mouth, and the process may extend down the pharynx and occasionally also the larynx. In many cases telangiectases, isolated or more compactly arranged, are found, but such appearances are hardly distinctive.

Instead of being colored a bright red, the lesions often assume a dusky red or bluish red color, and careful examination of such areas reveals frequently the presence of closely set telangiectatic vessels. In other cases there is superimposed an edematous element. This feature has clinical importance when there is implication of such structures as the larynx, and it may be an occasional cause of hoarseness, etc. In the mouth proper this bluish-red, edematous appearance is seen particularly in or near the margins of the gums, and such areas are prone to bleed readily. These lesions have been occasionally mistaken for scurvy or acute leukemia. In dermatomyositis there is no special predilection for the interdental papillae as is the case in scurvy. In a few instances the tongue may become more or less denuded of its epithelium, and such examples are occasionally regarded as pellagra.

The cases showing a widespread enanthem or severe subjective symptoms, such as profuse salivation, etc., are sometimes dignified by the title of stomatitis. The subjective complaints are best considered at the end of this section, for in many instances it is difficult to tell whether they are caused by changes in the mucous membranes proper or alterations in the deeper structures.

2 Simple Edema Without an Erythematous Component Occasionally this type of edema involves such portions of the mouth as the tongue, gums, soft palate, floor of the mouth, etc., and this phenomenon seems to be the counterpart of what is observed in the skin and the underlying tissues. This manifestation has special importance when it occurs in the glottis or other parts of the larynx.⁴⁰ In rare instances operative intervention by tracheotomy may be essential for the relief of obstruction to breathing.⁴¹ There may be mechanical difficulty in extruding the tongue which is swollen and painful, but this seems not to attain the degree of macroglossia observed, for example, in atypical amyloidosis, hemophilia, etc. The gums are occasionally swollen, and, when this is associated with bleeding, take on a spongy appearance simulating somewhat that seen in scurvy and acute leukemia.

3 Hemorrhage The bluish-red appearance of lesions in the mucous membranes is caused, for the most part, by dilatation of the superficial capillaries, and, as such, this appearance is not classed under the head of true hemorrhage. Extravasations of blood into the tissues in the form of purpuric spots or larger deposits are uncommon. Oppenheim¹⁰ recorded two cases in which "submucous sugillations" were observed in the cheeks, palate and posterior portion of the pharynx, with the subsequent formation of residual pigmented areas. In a few instances I have seen petechial spots, especially on the hard palate, and these lesions, which were generally few and isolated, may have represented traumatized and ruptured telangiectatic vessels. In any event, these petechiae possess no unusual clinical significance.

As noted previously, bleeding gums are sometimes encountered and in some cases small hemorrhages occur in other parts of the mucous membranes, including the nose. There is, however, no precise correlation between bleeding in the mucous membranes, the occurrence of purpura in the skin and the platelet count which is often but not always reduced. It is justifiable, therefore, to assume that local vascular damage, probably of a nonspecific type, is generally the important factor in the production of such hemorrhages.

4 *Vesicles* In some instances vesicular lesions bordered by a greater or lesser erythematous halo are observed on the tongue, gums, palate and other areas of the mouth. These manifestations often simulate ordinary aphthous stomatitis or herpes of the oral cavity. In some cases they are forerunners of eroded or more deeply ulcerated areas. The lesions are best remembered in a negative way.

5 *Erosions and Ulcerations* In dermatomyositis the mouth occasionally shows isolated or multiple, superficially eroded lesions occurring chiefly on the hard and soft palates, lips and tonsils, less commonly, on the nose and larynx. As in systemic lupus erythematosus, the borders are often colored a bright red to bluish-red, with many telangiectatic vessels which are not always easy to recognize. The eroded centers are covered with a whitish or yellowish membrane which is more or less adherent. When the lesions are isolated there is a decided resemblance to either aphthous stomatitis or to herpes. These alterations are similar to the oral manifestations in systemic lupus erythematosus, and in occasional instances, especially when the efflorescences are isolated, syphilis may be suspected.

In some cases the lesions may be deeply ulcerated. It is probable that this is owing not to any inherent attribute but more likely to secondary complications, such as superimposed infection. When such areas heal there are formed whitish depressed scars of variable size, up to that of a pea or larger, and such changes should not be confused with the leukoplakia-like alterations to be described in the next paragraph.

6 *Whitish Flat Areas (Leukoplakia-Like or Resembling Lichen Planus)* In my view this is one of the most important alterations found in the oral cavity in dermatomyositis. It has been observed by many investigators, myself included. Such changes are seen, especially on the cheeks, tongue and palate, as small areas, the size of a pea or larger, generally white or slightly yellow, with considerable resemblances to leukoplakia. However, in 10 cases of dermatomyositis Schuermann^{11b} failed to observe this lesion. In a review of the literature this investigator, impressed by the apparent restriction of this lesion to men in advanced life, concluded that it represented ordinary leukoplakia. This view cannot be accepted for the following reasons: (a) whereas most cases concerned men, a few instances occurred in women,¹² one of whom was a girl of 21; (b) in some instances the lesions were found in young persons.^{11c, 12} For example, in one case under my observation such patches were noted on the tongue in a young man who had a sore throat and in whom syphilis could be definitely excluded, thus the

lesions are capable of rapid spontaneous involution, as occurred in the aforementioned patient, (d) the favorite sites for leukoplakia, especially the angles of the mouth, are not affected, (e) the appearance of these lesions may not be limited to simple whitish areas, but in addition erythematous puncta and telangiectasia may be superimposed

Often the whitish areas are also arranged in the form of striae, lines or an irregular network, with considerable resemblances to lichen planus or lupus erythematosus. One or two examples recorded in the literature may well have been instances of lichen planus-like eruptions following the ingestion of arsenic, but in the vast majority of instances this factor can be safely eliminated from consideration. Each case must, therefore, be individualized in an effort to evaluate better this type of enanthem.

It is probable that the simple whitish lesions represent areas of localized hyperkeratosis analogous to those seen in relation to the proximal nail folds, which in the former situation are colored white, in the latter yellow, owing to anatomical peculiarities.

Subjective Symptoms Involvement of the mucous membranes is often associated with subjective complaints that may be not only disturbing but also serious. It is important to stress, however, that some of the symptoms may be dependent more directly on concomitant disease in the deeper tissues, for example, the muscles.

Increased salivary flow with its attendant phenomena is observed chiefly in cases showing ulcerated areas in the mouth or intense edematous infiltrations accompanied by oozing of the parts. This symptom may be caused alone or may be intensified by the simultaneous presence of disease in the muscles of swallowing, so that part of the secretion is exteriorized instead of being swallowed. In occasional instances the breath may be extremely fetid^{44, 45}. This is especially apt to occur when there is bleeding of the gums⁴⁵.

Xerostoma or dryness of the mouth is less commonly encountered. The mucous membrane of the mouth may be the site of a generalized bright erythema, whereas in other cases this symptom appears in the absence of objective signs. For the most part the precise cause of this manifestation is obscure, and there is no evidence that a deficiency of any of the vitamins is responsible. It is a phenomenon worthy of further study.

Difficulty in swallowing is often caused by the various lesions in the mucous membranes, especially those near the posterior aspect of the mouth. Rarely involvement of the tonsils plays a part. More important and probably more common than these as a cause of this symptom is the occurrence of muscular disease in the pharyngeal and perhaps other small muscles. This complaint is always to be regarded apprehensively owing to the danger of bronchopneumonia. In the occasional case in which recovery takes place despite muscular disease, it is likely that the alterations in the muscles were relatively mild in type. The interference with feeding, often a real problem in therapeutics in these patients, may be enhanced by involvement of the deeper tissues in the cheeks, which provide an additional obstacle to opening

the mouth and swallowing. Chewing of food is often impaired owing to the painful tension on the muscles concerned in this act.⁴⁶

Hoarseness is occasionally observed in dermatomyositis, and it arises from a variety of causes. Among these are involvement of the posterior portion of the throat by inflammatory or edematous infiltrations and similar changes in the larynx or in its muscles. Singly or combined, these may initiate the symptom or intensify it. Laryngeal edema of a high grade is an occasional cause of death.⁴¹ In some cases the voice takes on a peculiar husky quality,⁴⁷ and sometimes the speech is slow and monotonous. It is apparent that these symptoms may lead to confusion with a host of other diseases, such as myasthenia gravis, scleroderma, etc.

Pain in the mouth is generally owing to the presence of ulcerated areas or localized edematous infiltrations. A common site is the tongue, and here the symptom may occur as a result of involvement of the overlying mucous membrane, edema of the deeper parts of the structure or actual parenchymatous disease. Inability to protrude the tongue⁴⁸ from out of the mouth is a not uncommon occurrence. Struppler¹² observed an instance in which a swollen and painful tongue was the probable site of referred pain to the neck, but more commonly pain in the neck is owing to involvement of the deep pharyngeal or sternocleidomastoid muscles.

On the whole, the symptoms caused by the lesions in the oral mucous membranes are analogous to those encountered in many other diseases affecting the mouth.

Prognosis of Lesions in the Oral Mucous Membranes. V. Livonius,⁹ analyzing the records of 26 cases which showed involvement of the mucous membranes and in which the eventual outcome was known, found that death occurred in 12, or about 50 per cent of this group. An interesting point in this analysis was the practically invariable fatal outcome in those beyond the age of 50 years. These data did not impress Schuermann,¹¹⁶ for he noted a similar incidence of death in patients without involvement of the mucous membranes. Although this is true for the cases collected by Schuermann, it is unwise to accept the implications of this point of view. In mild examples of disease in the oral mucous membranes, the prognosis is probably not appreciably worsened. When these manifestations are more pronounced, especially in elderly persons, this must be regarded apprehensively owing to the possibility of a superimposed aspiration bronchopneumonia arising directly or as a contributory factor. The simultaneous occurrence of disease in the small muscles of the pharynx, etc., worsens the prognosis, although in occasional instances recovery may take place nonetheless.

Lips. The lips are sometimes sites of lesions in dermatomyositis. The most frequent manifestation is swelling of the parts, varying from a mild degree to the formation of projecting masses of tissue.¹¹⁷ Digital pressure produces pain, and this is especially likely to occur when the underlying tissue is complicated. Associated with the swelling there is often a hyperemia of the lips, or the epithelium may appear also, generally, a bright red

to dusky red areas,⁹ occasionally in the form of marmorization. When exudation is more intense, vesicles are sometimes seen and these may occur as crusted points. Ulcerations, the counterpart of those found in the oral cavity, are occasionally observed on the lips.¹⁰ As in the case of the oral mucosa, grayish-white streaks or even atrophic spots may be seen, although less commonly. Aside from the swelling which is generally greater than that in systemic lupus erythematosus, these manifestations are differentiated with difficulty, if at all, in these two diseases. As a rule, the changes in the lips, consisting of telangiectasia, erythema and varying degrees of atrophy, are more apt to be found in all forms of lupus erythematosus. The similarities to lichen planus of the lips may be mentioned in passing.

Tonsils Symptoms referable to the tonsils are sometimes encountered. These may occur at onset or during the course of dermatomyositis. Schuermann^{11b} recorded an instance in a girl of 12 in whom there were periodic swellings and redness of the tonsillar regions, and he was inclined to view this phenomenon as being more than a simple tonsillitis. In Bruce's⁵¹ second case the patient had, at onset, a slight sore throat accompanied by swollen cervical glands and a temperature of 103.5° F. In some cases there may be localized ulcerations, generally unilateral. Sheldon, Young and Dyke^{7c} reported one such example and noted, further, that there was no corresponding gland in the angle of the jaw. In still other patients the history seems to have indicated the occurrence of attacks of angina preceding the appearance of the more typical manifestations of dermatomyositis. It is of course difficult to be certain in such instances that this was actually caused by tonsillitis, for there are many other causes of sore throat in dermatomyositis.

On the whole, it appears that involvement of the tonsils, which occurs only occasionally, produces no signs or symptoms permitting differentiation from other diseases. It is still a question whether this is owing to a simple banal tonsillitis or is the result of inflammatory changes caused by dermatomyositis.

Conjunctiva A few instances of dermatomyositis have shown injected conjunctivae due chiefly to dilated capillaries, the equivalent probably of the telangiectases in the skin. Sometimes this causes a dark bluish-red appearance, especially in the palpebral parts. In rare cases there is a degree of blepharitis,⁵³ with discharge at the angles of the eyes, uncommonly tearing and photophobia.

The injected appearance of the palpebral portion of the conjunctiva is more often encountered in systemic lupus erythematosus, whereas in dermatomyositis it is not an especially important manifestation. Solid plaques of atrophy in this part of the conjunctiva are occasionally found in lupus erythematosus of the discoid atrophic form, but these have never been seen in dermatomyositis.

In an occasional case there may be pain in the upper lids on digital pressure, which is generally owing to disease in the muscles, especially the orbi-

cularis oculi ⁵⁴ In rare instances paralysis of the extra-ocular muscles may cause varying grades of ptosis or strabismus

Nose In addition to the various changes mentioned previously, there may be isolated edema of the nasal mucous membrane ^{11b} and the lower turbinates ⁵⁵ may be swollen In Potam's ⁵⁶ case the presence of an ulceration in the nasal cartilage was the chief basis for the diagnosis of glanders

(2) *Manifestations Associated with Disease in the Muscles and Subcutaneous Tissues* Dermatomyositis is generally regarded as a disease in which the muscles are chiefly affected, but often the subcutaneous tissue is simultaneously involved In most cases it is relatively easy to differentiate the manifestations caused by muscular disease In other instances this is more difficult and, for this reason, both structures are considered here jointly Whenever possible, an attempt will be made to show the respective influence of each

a Edematous Infiltrations The frequent occurrence of edematous infiltrations produces features that are distinctive, yet at the same time analogous with those found in other diseases Sometimes this obscures other striking manifestations and must therefore be dissociated from them

The edematous infiltrations affect large tracts of the limbs, chiefly in relation to the muscular masses although this is not always apparent The clinical features often seem to depend upon the stage of the illness, the depth of the extravasated fluid and perhaps other factors Early in the course the infiltration may be soft and pitting in type, later, firm and indurated, sometimes lairdaceous However, there seems to be no special rule, for the affected areas may show a doughy hardness from inception whereas in other cases the infiltration may be minimal and even apparently absent In nearly all instances of dermatomyositis, especially when the edematous element is pronounced, there is associated an intense degree of pain, and this painful edema is one of the outstanding features of this disease Often the overlying skin shows varying degrees of erythema and even a hemorrhagic component, but these manifestations may be absent or irregularly distributed

If the edematous infiltrations involve large portions of the limbs, it is the rule to find that the areas overlying the joints are spared or affected minimally This feature is a means of differentiating the edema of dermatomyositis from that of heart failure, save for those uncommon instances in which the former disease is accompanied by diminution in cardiac reserve Moreover, the edematous infiltrations in dermatomyositis seem not to produce the hide-bound tightening of the skin directly overlying such joints as the wrists, ankles, etc., a feature that appears to differentiate this disease from diffuse progressive scleroderma

The edematous element may be inconstant in the sense that such infiltrations may be conspicuous in one portion of the limbs or elsewhere and relatively inconspicuous in other parts of the same or other limb The latter may even at this time have reached the stage of evident atrophy of the muscles In the latter case also, the element of pain is attended by a deep

pressure on the atrophic muscles themselves, whereas in the former, a slight amount of pressure on the underlying tissues is all that is required to bring out evidence of pain. When the edematous infiltration is pronounced, it is often possible to show that the degree of pain on digital pressure increases as one proceeds from the skin to the subcutaneous tissue, and, finally, to the muscles themselves. In many cases lying in bed or turning from side to side is sufficient to provoke agonizing sensations, so that patients generally lie immobile and can hardly endure the weight of bed sheets. This picture of severe pain is the classical one described in texts, but there are many instances in which the edematous infiltrations and the painful element are minimal, even absent. Despite this, the muscular masses may progress toward atrophy. The latter course of events is seen especially in so-called poikilodermatomyositis which, as I have stated before, seems to be but a variant of ordinary dermatomyositis.

A. Phenomena Associated or Seen With Edematous Infiltrations 1 *Sign of Peau d'Orange* In occasional instances of dermatomyositis the edematous collections produce elevations of the skin surrounding the hair follicles, while the latter act as though they were anchored in situ, thus causing an exaggeration of the follicular openings with deepening of their apertures. This phenomenon, to which the above name has been assigned because of its resemblance to orange peel, is seen in many conditions involving an extensive infiltration of edematous fluid directly in the upper part of the skin. It is equivalent to the appearance seen in cancer of the breast in which it is caused either by a tremendous infiltration of cancerous tissue especially in the lymphatics or, according to Handley, by perilymphatic fibrosis. This phenomenon may be encountered, for example, when the skin is infiltrated with procaine. It is often seen in myxedema tuberosum circumscriptum and may be observed in scleredema adultorum of Buschke, especially when the skin is pinched up, and occasionally also in ordinary diffuse scleroderma in the early stages. I have observed it several times in dermatomyositis as a localized manifestation, especially on the limbs. It is an interesting but non-specific occurrence.

2 *Striae Atrophicans* In some instances of dermatomyositis the edematous infiltrations invade the cutis and cause stretching of the elastica fibrils, probably to the point of rupture. This manifestation may become evident only after the edematous collections have been resorbed in large part, and the phenomenon is analogous to what occurs in obese persons who lose weight rapidly. The striae are seen chiefly about the areas of joints or near them, as in a case that I reported^{1a}. It is probable that other areas may also be involved, for example, the abdomen, and in such a case there would be a close similarity with the striae found in association with pregnancy. The lesions in dermatomyositis seem not to be accompanied by hemorrhage and do not take on the bluish color seen so commonly in examples of "Cushing's syndrome."

3 *Calcification* Calcific deposits are often found in the subcutaneous tissues in dermatomyositis, less commonly in the muscles. When the process is more extensive or secondary infection is superimposed, the cutis may also be involved.

These deposits are found chiefly in the subcutaneous tissues where they arise probably as a consequence of local damage to the panniculus adiposus. They are observed principally in the limbs, especially about the joints, including the smaller articulations. The lesions are also commonly found independent of these parts, for example, in the buttocks, near the axillae, occasionally near tendons, etc. These deposits may be localized in one or several areas, but sometimes they are so extensive as to resemble the clinical picture of a universal calcinosis. In some cases they are symmetrically disposed. There may be small or large conglomerated masses the size of a fist or larger, but in many examples a radiologic examination is essential for their discovery. Ordinarily the calcific deposits occur as firm, often irregularly infiltrated, deeply situated nodules whereas the overlying skin is unaffected or may become adherent to the main mass. As they increase in size the cutaneous tissue becomes implicated and there may appear thinning of the skin with bluish discoloration. When these deposits break through the skin, they exude a dry mushy material of pasty consistence. Healing occurs with the formation of a depressed scar. Occasionally abscesses form, probably as a result of secondary infection, and the evolution of these lesions is like that of a warm cutaneous abscess,² with formation of a suppurative focus exuding calcareous pus. Healing is featured by atrophic cicatrices.

Extensive deposits of calcium, especially those near or in relation to muscular masses, may cause interference with movement or play of muscles. Calcific masses occur also within the muscles themselves^{72, 77} and are revealed, with great probability, by roentgen-ray examination. Rarely ossification apparently occurs, and in Bailey's patient⁷² this was surmised on the basis of an increased opacity in the skiagram showing lesions near the greater trochanters of the femora. Exceptionally, calcific deposits may be observed in other organs. For example, Gluck^{47a} recorded the occurrence of calcification not only in the subcutaneous tissues, but also in the laryngeal cartilage. Whether the latter was definitely related to or coincidental with the process of calcium deposition in the subcutaneous tissues, it is difficult to be certain. In any event, this association needs further study.

When the process is universally distributed in the subcutaneous tissues as in Randolph's case,⁷ the clinical picture often resembles closely that of ordinary universal calcinosis. When the deposits are restricted chiefly to the muscle, the features simulate myositis ossificans.

Subcutaneous calcification appears to be a nonspecific manifestation and may be encountered in a variety of diseases in which there is more or less extensive cutaneous involvement. Such lesions are not widely distributed and are not associated with systemic lupus erythematosus, myositis ossificans, or other conditions. It seems probable that other conditions, such as

wise to deduce etiologic relations between diseases on the basis of this phenomenon, even though in some of the affections named the pathogenesis of these deposits may be similar or even identical

Most observers agree that blood studies on the content of calcium and phosphorus reveal values within the range of normal. Sometimes the content of blood-calcium is actually diminished, although not to any striking degree. On the other hand, Petges and Petges² reported elevated values ranging from 13.5 to 15.5 mg and deduced from this a definite relation to hyperparathyroidism. On the whole, however, the evidence presented, including the data in the cases under my observation, appears to be at variance with this view. Moreover, it is my belief that this type of evidence cannot be used to support an alliance between dermatomyositis and scleroderma.

4 *Loss of Weight* Pronounced and often rapid wasting is frequently seen in dermatomyositis, this phenomenon generally being correlated with muscular disease. In some cases, however, implication of the subcutaneous fat contributes, partly at least, to an intensification of this phenomenon. During the stage of edematous infiltration and despite the rapid outpouring of fluid into the tissues, the weight may be below normal, and this becomes more manifest in cases showing improvement with resorption of the exuded fluid. Thus, in case 5 in a previous report¹⁰ wasting of the body became obvious following active diuresis.

At postmortem examination the subcutaneous fat may be absent,⁶⁰ atrophied,¹⁰ or replaced largely by fibrous tissue.⁶¹

It appears, then, that in many cases involvement of both the muscular and subcutaneous tissues contributes toward the rapid wasting so often seen in dermatomyositis and its congeners.

5 *Mucinous Deposits* In a few cases of dermatomyositis mucinous material has been found in the deeper cutis when special stains were used. The status of this phenomenon remains unclarified, most observers believing that it represents a degenerative product. It is found in a wide variety of conditions, including true myxedema of the skin, myxedema tuberosum circumscriptum, occasionally scleredema adultorum of Buschke and a number of cutaneous diseases.⁶² At present its occurrence is best regarded as a nonspecific phenomenon. The chemistry of mucin and the substances resembling it is in a state of flux. It is possible, although not certain, that the future may see means of differentiating these substances more satisfactorily.

6 *Electrocardiographic Changes* There is reason to believe that in occasional instances of dermatomyositis the electrocardiogram may show low-voltage owing to the increased resistance to the electric current imposed by edematous infiltrations of the muscles, subcutaneous tissues and even the skin.¹⁰ Such changes therefore cannot be regarded per se as positive evidence of myocardial disease but require correlation with the clinical features as is the case in myxedema with its electrocardiographic findings. In one instance the electrical resistance was so great that tracings could not be obtained until later in the course.⁶³ Apparently such manifestations are va-

riable in their appearance and are seen only in an occasional example of dermatomyositis

7 Total Protein in the Blood The present knowledge concerning the chemical properties of the edematous infiltrations in dermatomyositis is fragmentary, and investigations along these lines are clearly indicated. There is reason to believe that occasionally the total protein in the blood may be diminished as a result of the widespread effusions^{1b} and there is sometimes a tendency, although it is not especially striking, to a relative increase in the globulin fraction in the blood^{40c}

B Topographical Influences This section may now be completed with a more specific consideration of the changes produced in the clinical features in certain parts of the body owing to the pronounced degree of edematous infiltration. This is important for differential diagnosis.

1 Face In a previous section a characteristic facies was described. It was stated then that this may be modified or obscured by the occurrence of accessory edematous infiltrations in the deeper tissues of the face. In the latter event it is often difficult to tell whether the principal changes are in the muscles primarily or in the subcutaneous tissues, and sometimes it appears that both are affected. The clinical features depend not only upon the degree of edematous infiltration in the more superficial tissues and in the extent of muscular involvement, but also upon the stage at which the patient is observed. This explains, in part at least, the variability of the descriptions found in the literature on this subject.

In these cases the face is bloated, shiny, and the skin feels stretched and tense. Usually a brawny, nonpitting edema is found, and the skin may be pinched up with difficulty, if at all, from the deeper tissues. In one case under my observation^{1b} the edematous cheeks permitted pitting on digital pressure early in the course, whereas later these were sites of a firm indurated condition. As the lesion disappeared without residual sequelae, it seemed likely that the entire course of events could be explained on the basis of the type and degree of the edematous infiltration. Although the attributes of pitting on digital pressure and of lifting the skin in pliable folds are often characteristic and fairly constant in certain diseases, exceptions are apt to be encountered and the observer ought not to rely on hard-and-fast rules without knowing all the circumstances involved. Painfulness is also a variable symptom and may be replaced by a disturbing feeling of stiffness or tension in the parts.

When the edematous process in dermatomyositis is intense, the nasolabial folds are often almost or even completely obliterated. The tension on the tissues may be so great that the patient avoids talking or laughing⁴¹. All the other mimetic folds may also be obliterated, so that crying and smiling then make little change in the facial expression owing to the absence of normal wrinkling during the play of features^{42, 43}. Moreover, there may be difficulty in opening the mouth, an important factor in performing, with safety, the ordinary rules, the latter is caused chiefly by non-sterile evolution of

The foregoing data indicate that there may be considerable resemblance between the facial features of dermatomyositis and diffuse scleroderma, atypical amyloidosis, etc. Indeed, some observers have argued for an identity between dermatomyositis and scleroderma on the basis of such similarities. Yet, except in rare and incompletely studied cases, this differentiation is really not difficult. In dermatomyositis, for example, it is rare to find the facial phenomena induced by the "sclerotic" alterations seen in the average example of scleroderma, such as the typical pinched nose, almost beak-like, and the thin mouth with retraction of the skin away from the line of the teeth and the linear, often radiating fissures encountered especially on the upper lips. Difficulties in differential diagnosis arise only in exceptional examples of each disease when the surrounding tissues are secondarily implicated; in dermatomyositis, the subcutaneous tissue, in scleroderma, the muscles. In such instances, assuming that the clinical differentiation is beyond diagnostic acumen as far as the facial lesions are concerned, a close examination of the remainder of the course will generally permit resolution of the problem. A detailed study of the clinico-pathological differences between these diseases will be given in a succeeding publication.

2 Dorsa of the Hands The dorsa of the hands are often sites of edematous infiltrations, generally but not always accompanied by erythema of the affected parts. These infiltrations are similar in principle to those described on the limbs and face and show the same variable features already described. When the swellings and erythema are related to the tendinous structures and soft parts near the joints, for example the wrists, the observer may interpret this to mean involvement of the articulations. I have not seen in dermatomyositis the equivalent of the "frozen" wrists such as are commonly encountered in scleroderma. In some instances the edema is firm and doughy, interfering with closure of the hands and in such circumstances the resemblances to myxedema of these parts may be considerable.

3 Abdominal Region Occasionally the musculature and, perhaps also, the subcutaneous tissues over the anterior abdominal wall are affected by edematous infiltrations showing the same features already detailed^{1b, 47, 66}. Such manifestations may give rise to excruciating pains, and, unless interpreted properly, may be confused with intra-abdominal pathologic changes ("acute abdomen"). In cases involving large tracts of the abdomen, there may be resemblances to panniculitis of the abdominal wall⁶⁷.

b Rashes or Cutaneous Changes in Relation to Muscular Masses In some cases of dermatomyositis it is difficult to tell whether the cutaneous manifestations represent part of a widespread exanthem or whether these are more directly related to changes occurring in the deeper tissues, such as the muscles. In this section the discussion will be restricted to those instances in which the cutaneous manifestations seem to be related to disease in the deeper parts, as the muscles, and an attempt will be made to explain the inclusion of these appearances under a variety of titles.

It may be stated at the outset that examples of this disease in which the eruption is restricted to obviously affected deeper tissue are generally recorded under the title of polymyositis. There appear, however, to be transition between some of these cases and the variety showing the characteristic exanthem.

1 The edematous infiltrated and doughy muscular masses considered as typical of polymyositis (or dermatomyositis) are often surmounted by erythematous discolorations of variable extent and distribution. Where the erythemas are widespread or in the form of large tracts, these appearances generally go under the name of erysipelatoid redness, owing to the more or less vague resemblance to erysipelas of the limbs. Such cases have been recorded by many observers⁶⁸. These erythemas may also be transitory, relatively pale or speckled in appearance, slightly scaly, patchy or irregular in distribution, and may reveal minute capillary hemorrhages at the peripheries of patches or within them. These lesions are generally found on the extensor aspects of the limbs, but also frequently on the flexor surfaces, and occasionally in relation to the muscles of the trunk and other parts.

In other instances the patches assume a violaceous hue⁶⁹ or are colored a deep red. When such lesions are of limited size and are associated with pain in the underlying muscles, they may resemble closely erythema nodosum. The designation of phlebitis may be applied to such changes when they seem to lie in the line of veins. The term urticaria has occasionally been utilized in some cases for pale rosy, more or less transitory edematous infiltrations when the author really meant that these infiltrations were urticarial in type (major component being fluid in the tissues).

The purpose of this discussion, then, is to point out the necessity of designating accurately the cutaneous appearances, so that the literature may be freed, so far as possible, from extraneous names for manifestations readily explained on clinicopathologic grounds.

2 *Hypertrichosis*. Sometimes hypertrichosis of a localized type may be observed,^{70-72, 73, 74} chiefly in relation to the limbs, occasionally elsewhere. The occurrence of this curious phenomenon has led some observers to attribute it to an endocrine origin. In my view this manifestation arises from local causes, although the precise mechanism is as yet obscure⁷⁵. It is encountered in areas the sites of evident involvement of the deeper tissues accompanied often, although not always, by a degree of erythema in the skin. The inflammatory element, whether collateral or otherwise, seems to stimulate growth of hair, possibly through the medium of an increased blood supply or the presence of edematous fluid. It is of interest that a similar phenomenon has been noted occasionally in examples of myxedema tuberosum circumscriptum and it appears that the mechanism may be similar, if not identical, in the two conditions.

3 *Isolated Striae*. A few observers have described erythematous areas that apparently precede the eruption of tuberosa, especially those of the forearms or thighs^{76, 77}. Unilateral involvement of border areas

dermatomyositis and is one of the causes of contractures. It seems reasonable to infer that the cutaneous manifestations of this type may be related in some way to disease in the tendons, although in some cases these appearances seem to behave as though they were part of an exanthem. As this subject has received but scant attention, the matter must remain sub judice.

SKIN-MUSCLE RELATION

The association of cutaneous and muscular disease in the same patient is the fundamental background of the average example of dermatomyositis. It is not surprising, therefore, that observers have been deeply interested in the relation between these structures in this disease. Two principal views exist in this regard: (1) the eruptions represent a "collateral inflammatory element" in the sense of Tendeloo,^{11a} that is to say, the cutaneous changes are secondarily and completely dependent on the subjacent muscular disease⁷⁰, (2) the eruptions arise independently of alterations in the deeper tissues. In my view there is truth in both contentions, and it appears that each side has concerned itself only with its own particular observations. Sometimes the distinctions seem academic, but that arises chiefly because our present knowledge restricts definite decisions. It will be my purpose now to discuss the fundamentals of this controversy in greater detail.

1. A few observers, especially Schuermann,^{11b} have stressed the point that an interval of time often occurs between the appearance of the rash and clinical evidence of muscular disease. There are many cases in which the cutaneous lesions seem to appear some weeks, months, perhaps even years, before muscular phenomena are recognized. I can substantiate this point, but only in a general way, for there is at least one obstacle to its complete acceptance. Although this interval of time exists in a clinical sense, it is not at all certain that the muscles have actually been free of pathologic changes from the onset of the illness. This is the crucial point in the discussion, namely, that in the early stages when the eruption is conspicuous, the diagnosis is often overlooked and such instances are generally recorded as systemic lupus erythematosus, etc. O'Leary and Waisman³⁰ are inclined to believe that "in cases in which the onset is associated with a dermatosis sub-clinical muscular inflammatory changes are already present." Having seen a fairly large number of cases in the early stages, it seems to me that if the muscles were carefully palpated, evidence of their involvement would be forthcoming, certainly in a larger percentage than is generally recorded in this phase of the disease. However, it requires thorough search since only a few muscles may be affected at this time, and for this reason a biopsy specimen of muscle may fail to show alterations unless the proper site happened to have been chosen for this examination. On the other hand, there is reason to believe that our present knowledge of what are to be regarded as positive findings in biopsy specimens is not entirely clear. That is why a clinical approach with emphasis on the early cutaneous lesions is important.

2 Frequently there is a disproportion between the severity of the muscular changes and the cutaneous manifestations. Much weight has been laid on this point. However, this may be a fallacious argument in view of our lack of knowledge regarding the actual state of the musculature in such examples. It has long been known, for instance, that severe muscular changes may be encountered in patients with relatively little or even no symptoms referable to this tissue^{11c, 42a, 43a}. It has been suggested^{1b} that in such cases the edematous element, which is so closely associated with the complaint of pain, may be minimal in extent. The difficulties are further enhanced by the observation that the muscles may appear grossly normal, yet may present definite minute anatomical alterations.

3 Superficial lesions are often observed in areas devoid of underlying muscle, as for example, in the skin, over the knuckles, and in the mucous membranes on the hard palate and other parts. This is one of the best arguments for the dissociation of the exanthem and enanthem from disease in the muscles, but this conclusion holds mainly for the cutaneous and mucous membrane lesions described under the headings of exanthem and enanthem.

4 Many small muscles may be affected in areas in which there is no overlying skin, for example, the palatal muscles, diaphragm, etc. This argument has only restricted value.

5 The occurrence of cases in which the cutaneous lesions appear to be limited exclusively to sites of involved muscle affords evidence that in these instances, at least, a direct skin-muscle relation can be postulated reasonably. In these patients, however, the eruptions are generally not of the exanthematic type, but consist of dermatoses such as have been described at the head of this section. The few examples of tendon streaks may be mentioned here, but their pathogenesis must be left sub judice until additional data are forthcoming.

6 Finally, there seems to be a close anatomical relation between the blood supply of the muscles and the subcutaneous tissues, possibly also the lower portion of the cutis. However, information on the precise nature of this relation is surprisingly fragmentary.

From the data at hand, it is my belief that the alterations described in the category of exanthem and enanthem are best interpreted as phenomena occurring simultaneously and independently of the muscular changes, although both the skin and muscles are affected by the same etiologic factor. The other eruptions mentioned in this section seem to be closely associated with disease in the muscles and are apparently dependent upon the latter. When the affection strikes both systems with particular violence, it may be difficult to establish the nature of the relationship.

(3) *Miscellaneous Cutaneous Manifestations* The eruptions mentioned in this section generally have but little diagnostic importance and are often a confusing element. In many of the published accounts such dermatoses have been cited as important and essential lesions in dermatomyositis, but it

is my belief that this is not the case. Few observers seem to have considered these eruptions critically.

a Miliaria Crystallina This occurs occasionally in patients exhibiting abundant sweats in this disease. It is probable, however, that the importance of profuse sweating, originally stressed as an integral part of the symptomatology, has been exaggerated^{10, 16}. Its incidence, especially the severe bouts of sweating, appears to be much lower than the early reports in the literature indicate. Nevertheless, it does occur and is seen chiefly in severe cases of dermatomyositis requiring hospitalization, particularly those with high temperature. In some instances it seems to take the form of a "vasomotor" manifestation of unexplained nature. In such circumstances it becomes a phenomenon worthy of further study. Of itself it has no great value in differential diagnosis owing to its banality.

b Roseola In rare instances a small maculopapular eruption, occurring chiefly on the trunk as discrete spots, has been designated as a "roseola". Nearly all such examples have concerned cases in which the diagnosis of dermatomyositis was doubtful. Indeed, there is reason to believe that such instances may have been generally examples of trichinosis, a disease in which a roseola-like eruption is far more commonly encountered. In any event, the appearance of such lesions in the skin in dermatomyositis, if authenticated, is exceptionally rare. No such case has come under my observation and the more recent literature is completely silent on the point.

c Herpes Both herpes simplex and zoster are occasionally seen in dermatomyositis, also in systemic lupus erythematosus. These eruptions appear to possess doubtful value in differential diagnosis or prognosis. It is not rare to find a herpes simplex in association with a complicating pneumonic process in these diseases.

d Urticaria This is an uncommon manifestation in dermatomyositis⁷¹. In most instances the descriptions furnished would lead the critical observer to believe that these lesions were probably of the nature of more or less transient edematous infiltrations in the deeper tissues, such as the muscles and subcutaneous tissues. It may be mentioned, in passing, that true urticaria is an occasional accompaniment of trichinosis.

e Erythema Nodosum What applies to urticaria holds *pari passu* for erythema nodosum. In both, also, the incidental factor of drugs must also be eliminated as a possible cause, especially in these days of widespread use of sulfathiazol.

f Scarletiform Exanthem A few cases have been described in which the eruption at onset was diagnosed either as scarlet fever or a scarlatiniform exanthem^{71, 72}. It is probable that some of these, at least, represented the ordinary unrecognized eruption of dermatomyositis in a somewhat pronounced form. Whether the appearance is seen early or late in the course, it is always advisable to eliminate the possibility of other etiologic factors, especially drugs. Each case therefore requires individual study. On a

comparative basis trichinosis is more apt to show this type of dermatosis during its course. The rarity of this eruption in dermatomyositis and its obscure status do not warrant a place for it among the cutaneous manifestations of this disease, unless more convincing data are recorded in the future.

g "Erythema Multiforme" 1 Erythema Marginatum I have encountered two cases of dermatomyositis in which there were large plaques of marginated erythema chiefly on the limbs. In these instances the diagnosis of rheumatic fever had been originally suggested because of the eruption and the clinical features of "articular" pains, fever, sweating and, in one case, a high antistreptolysin titer, etc. Both concerned young persons in the second decade of life. Though there were some resemblances to the typical erythema marginatum rheumaticum, the eruption in dermatomyositis showed the following differences: (1) the limbs were the principal sites, the trunk being excepted. This is contrary to what is generally seen in the rheumatic type, though, it must be admitted, such localization does not entirely exclude the rheumatic variety, (2) more important, the individual marginated plaques in dermatomyositis remained visible in the same state for weeks or even months, whereas the cutaneous lesions in rheumatic fever are featured by transiency in the individual lesions.⁷⁵ This fundamental difference in behavior was helpful in placing the proper labels on these cases.

Undoubtedly such cases have been classified in the past as "muscular rheumatism," but the clinical course of the disease warrants separation of these two examples of dermatomyositis from the obscure syndrome encompassed within the term "muscular rheumatism."

2 Vesiculo-Bullous Erythema Multiforme The occurrence of scattered vesicles and bullae, sometimes of hemorrhagic type, in cases of dermatomyositis has often obscured recognition of the essential diagnosis. It has been pointed out³⁹ that the diagnosis of erythema multiforme, unless qualified in such a way as to designate a particular disease, is simply a morphologic description. There are times when our present knowledge does not permit more accurate classification of "erythema multiforme" but this difficulty will be overcome in future, as observers attempt to correlate such eruptions with the systemic manifestations.

h Cutaneous Hemorrhages Irregularly distributed purpuric spots, less commonly petechiae, are occasionally found in dermatomyositis. As in many other diseases, the lower limbs are often sites of such manifestations. The lesions are generally seen late in the course, occasionally early. In some instances there is an associated moderate grade of thrombocytopenia,^{10, 11b} but, as a rule, the relation of these hemorrhages to the hematologic formula, including the tourniquet test, bleeding time, coagulation time and clot retraction, is inconstant. There seem to be no clinical features by which these hemorrhagic manifestations can be distinguished from those seen in a host of other diseases.

Hemorrhages may also occur secondarily into other types of lesions, such as isolated vesicles or bullae, etc.

On the whole, these manifestations add a confusing element to the clinical picture and are best remembered in a negative way

a Ulcerations in the Skin These appearances arise in a number of ways

a Pressure sores (decubitus ulcers) are occasionally observed over the sacrum and other points of pressure^{71, 72} The factors contributing to their origin are the patient's immobility in bed for reasons mentioned and the probable poor local state of the tissues implicated These ulcerations are to be regarded apprehensively owing to the possibility that they may serve as a focus for a complicating bacteremia,⁷⁴ although healing may occur spontaneously⁷⁵

It is more common to observe ulcerations in scleroderma, especially over articular areas This is probably caused by the pressure of the hide-bound skin stretched tightly over the deeper contracted joints and the added factor of a deficient circulation to these parts More rarely, calcific deposits in the subcutaneous tissues or in the skin may break through to the outside

b The occurrence of ulcerations in the skin secondary to the pressure of calcific deposits in dermatomyositis or to superimposed infection of these foci has been previously mentioned, and likewise, the relatively common superficial erosions in the oral mucous membranes and the rare ulcerations in the nose and other parts

j Livedo Reticularis In an instance of dermatomyositis under my observation there appeared, as a sequel several months after the acute phase had been weathered, the cutaneous phenomenon classed as "livedo reticularis or racemosa" The lesions affected both the upper and lower limbs Originally regarded by Ehrmann⁷⁷ as a manifestation of syphilis, other observers began to record its occurrence in association with a host of other diseases In recent years, however, this eruption has been stressed as a manifestation of periarteritis nodosa⁷⁸ Without discussing the subject in any detail, it is my belief that these lesions represent a nonspecific eruption occurring in association with many diseases The question of whether the pathogenesis of livedo reticularis is the same or similar in all cases must be left open at present

SUMMARY

A detailed classification and discussion of the cutaneous and mucosal manifestations of dermatomyositis are given in terms of a clinicopathologic correlation Throughout the presentation an attempt has been made to indicate the essential differences from the eruption seen in systemic lupus erythematosus despite the many resemblances There is a typical dermatomyositic facies which may, however, be obscured by a number of factors Under the appropriate sections, also, reasons are given for the resemblances of dermatomyositis to such diseases as trichinosis, glomerulonephritis, sinusitis, pellagra, Addison's disease, scleroderma, scleredema adultorum, a spe-

cial type of panniculitis, acrodermatitis chronica atrophicans, epidermolysis bullosa and many other affections. In most instances the differential diagnosis is discussed fully, in others, due to limitations of space, a few essential points of difference are mentioned. A detailed analysis of the edematous infiltrations seen in dermatomyositis is given, together with a discussion of a number of phenomena associated or seen with these infiltrations. The nature of the skin-muscle relationship is considered and an attempt is made to clarify some of the obscurities involved in this fundamental subject.

BIBLIOGRAPHY

- 1 (a) KEIL, H. Dermatomyositis and systemic lupus erythematosus. 1. A clinical report of "transitional" cases, with a consideration of lead as a possible etiologic factor, *Arch Int Med*, 1940, lxxvi, 109.
- (b) Dermatomyositis and systemic lupus erythematosus. 2. A comparative study of the essential clinicopathologic features, *Arch Int Med*, 1940, lxxvi, 339.
- 2 PETGES, G, and PETGES, A. Poikilodermie, in *nouvelle pratique dermatologique*, Masson et Cie, Paris, 1936, vi, 114.
- 3 v LIVONIUS, E. W. Beitrag zur Kenntnis der Dermatomyositis, Berlin Thesis, 1938.
- 4 KEIL, H.: Parapsoriasis en plaques disseminees and incipient mycosis fungoides, *Arch Dermat and Syph*, 1938, xxxvii, 465.
- 5 KEIL, H. Conception of lupus erythematosus and its morphologic variants, with particular reference to "systemic" lupus erythematosus, *Arch Dermat and Syph*, 1937, xxxvi, 729.
- 6 KEIL, H. Relation between "systemic" lupus erythematosus and a peculiar form of thrombocytopenic purpura, *Brit Jr Dermat*, 1937, xlix, 221.
- 7 CAUSADE, L, and ALESHKOWSKA, S. Polymyosites rhumatismales de l'enfance, *Paris méd*, 1933, lxxxix, 469.
- 8 PETGES, P. B. A. Poikilodermie et poikilodermatomyosite, Thèse de Bordeaux, 1929-1930.
- 9 OPPENHEIM, H. Zur Dermatomyositis, *Berl klin Wchnschr*, 1899, xxxvi, 805.
- 10 OPPENHEIM, H. Über die Polymyositis, *Berl klin Wchnschr*, 1903, xl, 381.
- 11 (a) GOTTRON, H. Hautveränderungen bei Dermatomyositis, VIII Congress International de Dermatologie et de Syphilographie, Aug 5-9, 1930, Copenhagen, p 826.
- (b) SCHUERMANN, H. Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), *Arch f Dermat u Syph*, 1939, clxxviii, 414.
- (c) BRUUSGAARD, E. Poikilodermie mit Polymyositis, *Zentralbl f Haut u Geschlechtskr*, 1933, xliii, 432.
- (d) FUHS, H. Über Poikilodermatomyositis und ihre Stellung im System der Hautkrankheiten, *Arch f Dermat u Syph*, 1933, clxviii, 505.
- (e) ZON, J. J. Dermatomyositis und Poikiloderma Jacobi mit Muskelveränderungen, *Arch f Dermat u Syph*, 1934-35, clxxi, 223.
- 12 MILIAN, G, and RIME. Érythème scléro-oedémateux avec myopathie et myasthénie, *Bull Soc franc de dermat et de syph*, 1925, xxxii, 470.
- 13 LORTAT-JACOB. discussion under reference 12.
- 14 STRENG, W. Ueber Polymyositis, *Ztschr f klin Med*, 1904, liii, 162.
- 15 PICK, W. Dermatomyositis, *Arch f Dermat u Syph*, 1935, clxxiii, 302.
- 16 WARSZEWSKI, E. H., and RADZINSKI, J. M. Subacute polymyositis, *Illinois Med Jr*, 1937, lxxi, 351.
- 17 DOWLING, G. B. Dermatomyositis, *St Thomas Hosp Rep*, 1936, i, 150.
- 18 SEMON, H. Case of poikilodermatomyositis, *Brit Jr Dermat*, 1937, xlix, 120.

- 19 BAMBER, G Poikilodermatomyositis, Proc Roy Soc Med (Sect Dermat), 1936, *xxix*, 1635
- 20 URBACH, E Über Stauungs- und Stoffwechselkeratosen, Arch f Dermat u Syph, 1936, *clxxix*, 400
- 21 KRIE, H The rheumatic subcutaneous nodule and simulating lesions, Medicine, 1938, *xvii*, 261
- 22 WEIDMAN, F D, and BISANCON, J H Erythema elevatum diutinum, Arch Dermat and Syph, 1929, *xx*, 593
- 23 WEIDMAN, F D Personal communication kindly sent to the author, May 7, 1940 Dr Weidman stated that he had no additional information on the further course of his second patient
- 24 GATELY, J E, and KETTON, L W Erythema elevatum diutinum (Weidman), Arch Dermat and Syph, 1939, *xxxix*, 901
- 25 URBACH, E Extracellular cholesterosis, in Handbuch d Haut u Geschlechtskr, 1932, *xii*, 320
- 26 TOWLE, H P Dermatomyositis, Arch Dermat and Syph, 1936, *xxxiv*, 298
- 27 MCCARTHY, F P Discussion of reference 26
- 28 Mayo Clinic (Dermatologic Department) Dermatomyositis (a group of cases), Arch Dermat and Syph, 1937, *xxv*, 984
- 29 HENDRI, A W, and ANDERSON, T E Dermatomyositis, Lancet, 1939, *ii*, 80
- 30 O'LEARY, P A, and WAISMAN, M Dermatomyositis, a study of forty cases, Arch Dermat and Syph, 1940, *xli*, 1001
- 31 INGRAM, J T, and STEWART, M J Dermatomyositis and poikiloderma, Brit Jr Dermat, 1934, *xlvi*, 53
- 32 BAILEY, R H Dermatomyositis complicated by calcinosis, Proc Royal Soc Med (Sect Study of Disease in Children), 1937-38, *xxxii*, 1155
- 33 SCHATZKI, R Beitrag zur Frage der Dermatomyositis (Polymyositis acuta), Berlin Thesis, 1926
- 34 CREVALD, S VAN Ein Fall von Polymyositis acuta, Ztschr f Kinderheilk, 1929, *xlvi*, 74, 1930, *xlix*, 357
- 35 DOHI, S A case of poikiloderma atrophicans vascularis, Zentralbl f Haut u Geschlechtskr, 1929, *xiv*, 451
- 36 WOLF, A, and WILENS, S L Dermatomyositis, a report of two cases with complete autopsy, Am Jr Path, 1936, *xii*, 235
- 37 ENGELHARDT, W Dermatomyositis (?), Poikiloderma vascularis atrophicans (?), Zentralbl f Haut u Geschlechtskr, 1935-36, *liii*, 69
- 38 MEMMERT, H P W Schleimhautveränderungen bei Dermatomyositis, Berlin Thesis, 1938
- 39 KEIL, H Erythema multiforme exsudativum (Hebra), a clinical entity associated with systemic features, ANN INT MED, 1940, *xiv*, 449
- 40 (a) MARCUS, I H, and WEINSTEIN, J Dermatomyositis, report of a case with a review of the literature, ANN INT MED, 1935-6, *ix*, 406
 (b) GOTTSTEIN, E Über Polymyositis, Deutsch Arch f klin Med, 1907, *xcii*, 198
 (c) LANE, C W Dermatomyositis, South Med Jr, 1938, *xxxi*, 287
- 41 STRUPPLER, T Zur Pathologie der multiplen nichteitrigen Myositis, Deutsch Arch f klin Med, 1900, *lxviii*, 407
- 42 MULLER, R Atrophoderma erythematodes reticularis (Poikiloderma atrophicans vascularis Jacobi), Arch f Dermat u Syph, 1911, *cix*, 501
- 43 (a) GLUCK, A "Dermatitis atrophicans reticularis" (Poikiloderma atrophicans vascularis Jacobi) mit mucinöser Degeneration der kollagenen Fasern, Arch f Dermat u Syph, 1913-14, *caviii*, 113
 (b) BETTMANN, S Über die Poikiloderma atrophicans vascularis, Arch f Dermat u Syph, 1920, *cxxix*, 101

- 44 STRUMPELL, A Zur Kenntnis der primären acuten Polymyositis, *Deutsch Ztschr f Nervenheilk*, 1891, 1, 479
- 45 BENSON, J R A case of dermatomyositis, *Clin Jr*, 1904, xxiv, 315
- 46 SCHWARZ, R Beitrag zur Aetiologie der Polymyositis, *Frankf Ztschr f Path*, 1921, xlv, 141
- 47 SLUCZEWSKI, A Ueber einen Fall von Dermatomyositis, *Dermat Ztschr*, 1931, lxi, 390
- 48 JACOBY, G W Subacute progressive polymyositis, *Jr Nerv and Ment Dis*, 1888, xv, 697
- 49 STEINFELD, F Zur Kenntnis der Dermatomyositis, *Deutsch med Wchnschr*, 1930, lxi, 697, 959
- 50 BEZECNY, R Dermatomyositis, *Arch f Dermat u Syph*, 1934-5, clxxi, 242
- 51 BRUCE, G M Retinitis in dermatomyositis, *Trans Am Ophth Soc*, 1938, xxxvi, 282
- 52 SHELDON, J H, YOUNG, F, and DYKE, S C Acute dermatomyositis associated with reticuloendotheliosis, *Lancet*, 1939, 1, 82
- 53 GREENAWAY, T M, LAMBIE, C G, THOMSON, E, and DAVIES, G S Dermatomyositis, *Brit Jr Dermat*, 1937, xlix, 209
- 54 SCHMAUTZER, J Ueber Polymyositis acuta, *Med Klin*, 1914, x, 281
- 55 LORENZ, H Die Muskelerkrankungen, in H Nothnagel's *Spec Path u Therapie*, Theil 3, 1898, xi, A Holder, Wien
- 56 POTAIN, C Morve chronique de forme anormale, *Bull et mém Soc med d hôp de Paris*, 1876, xii, 314
- 57 (a) KERL, W Dermatomyositis, *Zentralbl f Haut u Geschlechtskr*, 1936-7, lv, 179
(b) HAMMES, F Polymyositis chronica, ein Beitrag zum Symptomenbild derselben, *Med Klin*, 1920, xvi, 872
- 58 RANDOLPH, C C Calcinosis universalis und dermatomyositis, *Jr Pediat*, 1934, iv, 342
- 59 (a) O'LEARY, P A Discussion in reference 28
(b) FRENCH, H An index of differential diagnosis of main symptoms, 4th Ed, 1928, p 701, W Wood & Co, N Y
- 60 STEINITZ, H, and STEINFELD, F Untersuchungen zum Kreatinstoffwechsel bei Dermatomyositis, *Ztschr f d ges exper Med*, 1931, lxxix, 319
- 61 BATTEN, F E Case of dermatomyositis in a child with pathological report, *Brit Jr Child Dis*, 1912, ix, 247
- 62 SCHUERMANN, H Ueber Hauterscheinungen mit Beziehung zu Myxodem und basedowischer Krankheit, *Arch f Dermat u Syph*, 1937-8, clxxvi, 544
- 63 Case seen at the Newark Beth Israel Hospital, service of Dr A E Parsonnet, through the courtesy of Drs H H Goldberg and W Antopol
- 64 GRZYBOWSKI, M Zur Kenntnis der Dermatomyositis, *Arch f Dermat u Syph*, 1936, clxxiv, 541
- 65 OGILVIE, W H Three cases of myositis, *Proc Royal Soc Med (Section of Orthopedics)*, 1923-4, xvii, 7
- 66 CORNBLEET, T, and MURPHY, E L A case for diagnosis (dermatomyositis), *Arch Dermat and Syph*, 1937, xxxvi, 647
- 67 KEIL, H Panniculitis—its place in nosology, *Brit Jr Dermat*, 1935, xlvii, 512
- 68 (a) VERON, L Observation de myosite infectieuse aigue, *Arch de med et pharm mil*, 1888, xi, 481
(b) BUSS Ein Fall von acuter Dermatomyositis, *Deutsch med Wchnschr*, 1894, xx, 788
(c) VINCENT, H Polymyosite infectieuse aigue a recidives, *Bull et mem Soc méd d hôp de Paris*, 1903, xx, 633
(d) MÉRZY, TERRIEN, and GÉNEVRIER Polymyosite infectieuse aigue benigne chez un enfant de neuf ans, *ibid*, 1904, xxi, 1115
(e) DRAGOEWAL, N Polymyositis acuta und Trichinose, *Berl klin Wchnschr*, 1919, lvi, 316

- 69 (a) PUIMOTIER, F Über Dermatomyositis, Deutsch Ztschr f Nervenheilk, 1921, lxxiii, 370
(b) OPPENHEIM, H Lehrbuch der Nervenkrankheiten, 7th Ed, 1923, vol 1, p 840, S Karger, Berlin
(c) KILB H Personal observations
(d) GOTTRON H Dermat. Ztschr, 1931, lxi, 415
- 70 ГАЙК, Г Zur Frage der Polymyositis (Dermatomyositis), Arch f Dermat u Syph, 1921, cxv, 1
- 71 WEIT-KARLIS S A case of polymyositis with multiple lime deposits in a boy 5 years of age, Med Rec, 1913, lxxviii, 1052
- 72 (a) SHILDON, I H, and SHILDON, W Dermatomyositis, Proc Royal Soc Med, 1931-32, xxv, 413
(b) KNIFRIM, H Über akute, nicht eitrige Polymyositis, Deutsch Ztschr f Nervenheilk, 1913, xlvii, 297
- 73 KEIL, H The rheumatic erythemas, a critical survey, ANN INT MED, 1938, xi, 2223^{*}
- 74 (a) KARELITZ, S, and WELT, S K Dermatomyositis Am Jr Dis Child, 1932, xliii, 1134
(b) EVANS P R Case of dermatomyositis, Brit Jr Dermat, 1937, xlv, 122
- 75 EHRMANN, S Ein neues Gefassymptom der Syphilis, seine Beziehung zur Cutis marmorata, zum grossmakulösem Syphilid und zur Spirochaeta pallida 6th International Dermatologic Congress, New York, 1908, p 763
- 76 KETRON, L, and BERNSTEIN, J C Cutaneous manifestations of periarteritis nodosa, Arch Dermat and Syph, 1939, vi, 929

MULTIPLE TESTS OF HEPATIC FUNCTION IN GASTROENTERIC MALIGNANCY; THE VALUE OF BROMSULPHALEIN, HIPPURIC ACID AND THE VAN DEN BERGH REACTION IN DETECTING HEPATIC METASTASIS, WITH AN EVALUATION OF NORMALITY OF THE HIPPURIC ACID TEST *

By MOSES PAULSON, M D , F A C P , *Baltimore, Maryland*, and
CARL I WYLER, M D , *Cincinnati, Ohio*

FROM time to time throughout the past years communications have appeared which have indicated that the prediction of the existence of hepatic metastasis was a possibility. In 1925 Rowntree and his associates¹ using phenol tetrachlorophthalein concluded that "in the absence of clinical evidence of hepatic involvement the phenoltetrachlorophthalein test may furnish the only evidence of the existence of metastatic nodules in the liver." Positive tests were not obtained in all cases of metastatic involvement. Bargen and Rankin,² in 1930, felt that their results, using bromsulphalein and the van den Bergh test in carcinoma of the large bowel, were statistically indicative although again there were individual exceptions. In 1935 Wever, Althausen and Biskind³ attacked the problem using the Rose Bengal test together with icterus index and glucose tolerance. In 33 cases of secondary hepatic neoplasm, 26 showed some degree of dye retention. The negative side of the problem, i.e., results in patients without metastasis, was not discussed. Meranze, Meranze and Rothman,⁴ using the Bodansky alkaline phosphatase determination,⁵ found an excellent correlation between elevated phosphatase levels and hepatic metastasis. Gutman, Olson, Gutman and Flood,⁶ commenting on this work, agreed with its general validity but point out again that errors may occur in patients both with and without metastasis.

It was with this literature in mind that we decided to determine whether application of the hippuric acid synthesis to this problem would be of benefit. Accordingly this test was performed, together with the bromsulphalein determination and the quantitative indirect van den Bergh reaction, on a number of patients with malignant disease. The necessity for the use of multiple tests in the evaluation of liver function status and the fact that disorder of function may appear more evident in one modality than in another are well appreciated.

MATERIAL

The patients investigated were individuals who clinically and roentgenologically were thought, prior to surgery, to have malignancy of the

* Received for publication July 13, 1941

From the Gastrointestinal Section and Laboratories of the Medical Clinic of the Johns Hopkins Hospital and University, Baltimore

stomach or the colon. We restricted ourselves to these sites of origin because such tumors are well known to involve the liver early by metastasis. No patients with palpable livers, jaundice, or any other evidence of either liver disturbance or metastasis elsewhere were included in our group. When metastases are described subsequently as present or absent this denotes whether or not they could be seen or felt by the operator several days later.

METHOD

The hippuric acid determinations were done as described by Quick,^{7,8} using the intravenous method. This was necessary since some of the patients were undergoing gastric aspiration in preparation for surgery at the time determinations were done. The studies were started before we were aware of the modification proposed by Weichselbaum and Probst,⁹ and it did not seem advisable to change our technic once we had started. However, we made use of their work by adopting as the solubility factor 0.0055 gm per c.c. which is their average finding, rather than the 0.0033 originally suggested by Quick. It is possible that several of the cases with zero excretion actually would have shown some precipitation if salting out had been resorted to, although they obviously would have been quite low. Nitrogen retention was not present in those cases with low figures.

The bromsulphalein test of Rosenthal and White¹⁰ is too well known to require any further description. It should be noted, however, that the 5 mg./kilo dosage was used throughout and that all determinations were made one-half hour after intravenous injection.¹¹

The indirect quantitative van den Bergh reaction requires no comment.

RESULTS

Table 1 shows the results on 25 consecutive patients with malignancy. Study of this table reveals several things. It is apparent that, although the bromsulphalein test is of considerable value in the prediction of metastasis, the correlation is not perfect. We did not anticipate normal tests invariably in the absence of metastasis, since there is no reason why preexisting liver damage could not cause an abnormal test in the absence of metastasis. However, at least two cases (12 and 15) showed metastasis with bromsulphalein excretion at normal levels.

The van den Bergh test proved of no value other than to exclude icterus chemically as had already been done clinically.

There is no correlation whatsoever between the level of hippuric acid excretion and the presence of metastatic hepatic lesions. It is true, though, that a complete absence of hippuric acid by the method used was in every instance associated with metastatic involvement (six cases). What did intrigue us, however, were the uniformly low levels of hippuric acid excretion which we obtained in this series. With three exceptions the results are below the normal of 1.00 to 1.40 grams of hippuric acid (following the

TABLE I

No	Patient	Age	Sex	Site of tumor	Met to liver	vdB units	B S P	Hipp Acid	Remarks
1	LS	61	F	rectum	No	0.2	5%	1.00	Normal hipp acid
2	PP	51	M	hepatic flexure	No	0.3	5%	0.93	
3	EJ	33	F	rectum	No	0.2	5%	0.87	Single nodule in liver Normal hipp acid
4	JA	62	M	stomach	No	0.3	5%	0.80	
5	PG	48	M	stomach	No	0.3	5%	0.79	
6	EC	55	M	stomach	No	0.2	5%	0.63	
7	AS	49	M	cecum	No	0.4	5%	0.62	
8	JL	53	M	stomach	No	0.3	5%	0.60	
9	GW	51	F	sigmoid	No	0.4	5%	0.54	
10	CP	57	M	stomach	No	0.2	5%	0.51	
11	HG	67	M	stomach	No	0.3	5%	0.44	
12	TS	68	M	cecum	Yes	0.3	5%	0.00	
13	BW	58	M	stomach	No	0.5	10%	1.08	Small scattered nodules Peritoneal implants, liver relatively free Tumor adhered to liver, pancreas, spleen
14	JL	51	M	stomach	No	0.3	10%	0.91	
15	WA	42	M	stomach	Yes	0.75	10%	0.41	
16	MS	42	F	stomach	Yes	0.5	15%	0.87	
17	BM	58	M	stomach	Yes	0.5	15%	0.51	Scattered nodules Widespread Normal hipp. acid
18	JR	66	F	rectum	Yes	0.5	15%	0.39	
19	HW	73	F	sigmoid	Yes	0.4	15%	0.00	
20	SB	40	F	transv colon	No	0.2	20%	1.13	
21	HB	72	F	stomach	No	1.25	20%	0.44	Scattered nodules Widespread
22	AL	65	M	rectum	Yes	0.2	20%	0.00	
23	BM	48	F	transv colon	Yes	0.3	25%	0.00	
24	RJ	66	M	stomach	Yes	0.3	30%	0.00	Widespread Widespread
25	LL	52	M	sigmoid	Yes	0.75	40%	0.00	

intravenous administration of 1.77 grams sodium benzoate) as suggested by Quick^{7,8} and confirmed in adults by Weichselbaum and Probst⁹, Mateer, Baltz, Marion, and Holland,¹² and others¹³

As a possible explanation of this, it occurred to us that the normal for this test had probably been determined on healthy young adults. It is also our experience that "normal" levels are almost always attained in the usual healthy youth. We could find no record, however, of the test's having been applied to individuals in the middle and late decades of life—to individuals who had no evidence of or obvious cause for hepatic damage. Therefore, we decided to apply exactly similar tests to a group of hospital patients of approximately the same age and sex distribution who did not have carcinoma, who had no obvious cause for or sign of hepatic disease or dysfunction, and who were essentially free of digestive complaints. As the accompanying chart shows, however, these patients suffered from various major illnesses and, although the outcome was favorable in the majority of instances, the patients at the time they were studied were moderately or severely ill. The results of this study are shown in table 2. It can be seen that, although in this group seven of the cases attain normal figures and several others are quite close to that level, at least 16 of the 25 patients showed a deficit in the synthesis and excretion of hippuric acid of a degree which is ordinarily con-

sidered to signify impaired hepatic function. This is particularly striking inasmuch as 23 of the 25 patients had a completely normal excretion of bromsulphalein. Although we do not by any means wish to compare procedures evaluating dissimilar functions, it is our common experience and that of others that clinically significant liver damage is very frequently accompanied by a reduction in bromsulphalein excretion. In none of these cases was a significant elevation of the van den Bergh test encountered.

TABLE II

No	Patient	Age	Sex	Diagnosis	BSP	vdB	Hipp Acid	Remarks
1	L K	28	F	Acute arthritis, type undetermined	5%	0.1	1.33	Normal hipp acid
2		43	M	Acute psoriasis	5%	0.4	1.23	Normal hipp acid
3	J C	51	M	Pneumonia Pneumo I	5%	0.5	1.23	Normal hipp acid
4	M P	26	M	Acute rheumatic fever	5%	0.2	1.22	Normal hipp acid
5	C L	33	M	Gon arthritis, acute	5%	0.2	1.20	Normal hipp acid
6	B J	43	F	Acute rheumatic fever	5%	0.3	1.18	Normal hipp acid
7	P C	53	M	Sarcoid	5%	0.4	1.13	Normal hipp acid
8	E W	61	M	Auricular fibrillation with mult emboli	5%	0.2	0.98	
9	I Z	49	F	Nephrosclerosis	5%	0.2	0.96	No nitrogen ret
10	U B	47	M	Subacute bacterial endocarditis	5%	0.3	0.85	
11		56	F	Pneumonia conv	5%	0.3	0.85	
12	L B	46	F	Subacute bacterial endocarditis	5%	0.2	0.73	
13	C W	59	M	Active rheumatoid arthritis	5%	0.3	0.67	
14	M W	68	F	Pneumonia Pneumo I	5%	0.4	0.58	
15	O W	42	M	Coronary occl No failure	5%	0.5	0.57	
16	E G	57	F	Acute rheumatoid arthritis	5%	0.3	0.55	
17	C H	61	F	Pneumonia Pneumo V	5%	0.3	0.53	
18	C J	59	F	Neurologic dis with muscle atrophy	5%	0.2	0.53	
19		51	F	Arthritis acute type undeterm	5%	0.3	0.48	
20	P R	55	M	Coronary occl No failure	5%	0.3	0.44	
21	P B	39	M	Asthmatic bronchitis, bronchopneumonia	5%	0.3	0.38	
22	L T	41	F	Avitaminosis due to inadequate food intake	5%	0.4	0.32	
23	M D	29	M	Polycystic kidney with impending uremia	5%	0.2	0.32	
24	E F	54	M	Pneumonia no type	10%	0.2	0.45	Mod alcohol ingestion
25	I S	60	F	Bronchiectasis with bronchopneumonia	15%	0.2	0.00	Had had antilutetic treatment

It is interesting to speculate on possible explanations for these consistently low figures of hippuric acid excretion. First, it is considered possible that the procedure is not entirely a test of liver function. Best and Taylor¹⁴ state (without giving evidence) that formation of hippuric acid from benzoic acid and glycine takes place in the kidneys as well as in the liver. The kidneys are known to be principally concerned with this function.

in the dog at least. Although none of the patients tested had an abnormal degree of nitrogen retention, it is still conceivable that renal damage may have influenced the results.

Although the test is performed with the patient fasting or after partaking of only a light meal, it seems obvious that the patient's nutritional state at the time of testing may modify the results—this in spite of the body's known ability to synthesize glycine. We have indeed found this to be true in several cases—the amount of acid obtained rising as a dehydrated and malnourished individual with a gastric carcinoma is hydrated, transfused and prepared for surgery.

It may also be suggested that the low figures are, in fact, an expression of actual hepatic dysfunction and that this may indeed in some of the acutely ill subjects be a temporary thing. Haines, Magath and Power,¹⁵ who investigated the hippuric acid test in thyrotoxicosis, have noted that "it seems probable that marked alterations in the test can occur because of functional changes in the liver that must be of short duration and temporary." It is certainly true that when patients with many of the diseases enumerated in table 2 are seen at the autopsy table, microscopic abnormalities are found in the liver.

Whatever may be the cause of these results, practically it is important to point out that they do not necessarily signify important primary disease of the liver. The normal bromsulphalein excretion encountered almost throughout table 2 is in line with clinical findings. Haines and his co-workers¹⁵ also noted in their study that, although there was some correlation in hyperthyroidism between bromsulphalein retention and reduction of hippuric acid output, there were frequent exceptions, with a normal bromsulphalein and considerable reduction of hippuric excretion. They concluded, in addition, that the test was of little value in pre-operative determination of the patient's fitness for surgery in thyrotoxicosis. Whether the hippuric acid excretory level would rise toward that figure considered normal in many of those individuals in table 2 who made essentially complete recoveries from acute illnesses is something which at present we are not able to answer.

It becomes apparent from a consideration of these data that increased sensitivity in tests of hepatic function, which has been a prime desideratum of investigators in this field, can definitely be carried beyond practicable limits. Tests can become so delicate that insignificant or transient degrees of dysfunction are detected by them. In this way the result of the test loses its significance and the procedure fails as a diagnostic measure by drawing attention to the liver in undiagnosed disease, when this gland is not primarily or even importantly involved. Hepatic function tests of greatest value may be thought of as occupying a relatively narrow band of sensitivity with tests of less clinical value ranged on either side. The most highly sensitive tests, of course, may be of considerable value when used serially in recording progressive change in condition and prognosis.

It should be obvious that the statements and discussion above have nothing to do with those tests used in differentiating intra- and extrahepatic icterus

SUMMARY AND CONCLUSION

Hippuric acid, bromsulphalein and van den Bergh tests were done on 25 patients with carcinoma of the stomach or colon who had no clinical evidence of metastasis. A correlation was found to exist between the presence of gross hepatic metastasis, as determined at subsequent operation and the degree of bromsulphalein retention, although individual exceptions occurred. No significant correlation was found between the presence of metastasis and the amount of hippuric acid excreted. However, in all six cases in which no hippuric acid was found metastases were present. The van den Bergh was not of diagnostic aid.

Owing to the uniformly low levels of hippuric acid excretion found in these cases of carcinoma, a second series of 25 patients of comparable age and sex distribution was tested. This latter group was composed of individuals who had no signs, symptoms, or good historic reason for hepatic damage but who were suffering from a wide variety of acute and chronic diseases. Sixteen of these patients showed lowering of the hippuric acid synthesis below the level considered as normal, although in 23 of the 25 cases the bromsulphalein excretion was entirely within normal limits. Possible explanations for this difference are discussed. It is suggested that extreme delicacy in tests of hepatic function may detract from their importance as diagnostic aids by too frequently giving abnormal results in cases in which liver damage is slight and is a relatively unimportant part of the general clinical picture. This in no way invalidates the serial use of the most delicate tests in following the course of liver disease and in so determining prognosis. Neither do the above statements apply to those tests used in the differentiation of intrahepatic from extrahepatic icterus.

This concept (that liver function tests can fail if too sensitive) is somewhat different from that usually held, in which it is felt that the failure of tests of hepatic function is primarily owing to their grossness.

We wish to thank Eloise White Gould for her technical assistance and Dr. August F. Jonas, Resident Surgeon, for his kindness in putting the surgical material at our disposal.

BIBLIOGRAPHY

- 1 GREENE, C. H., McVICKER, C. S., WALTERS, W., and ROWNTREE, L. G. Diseases of the liver. IV. Functional tests in cases of carcinoma of the liver and biliary tract, *Arch. Int. Med.*, 1925, **xxxvi**, 542-560.
- 2 BARGEN, J. A., and RANKIN, F. W. Tests of hepatic function in carcinoma, their value in cases of neoplasm of colon with and without metastasis to liver, *Ann. Surg.*, 1930, **xc**, 225-232.
- 3 WEVER, G. K., ALTHAUSEN, T. L., BISKIND, G. R., and KERR, W. J. Liver function in hepatic and extrahepatic diseases, results of clinical experience with 326 cases, *Am. Jr. Digest. Dis. and Nutr.*, 1935, **ii**, 93-99.

- 4 MERANZE, D R, MERANZE, T, and ROTHMAN, M M Serum phosphatase as an aid in diagnosis of metastasis of cancer to liver, *Pennsylvania Med Jr*, 1938, xli, 1160-1164
- 5 BODANSKY, A Phosphatase studies, determination of serum phosphatase Factors influencing accuracy of determination, *Jr Biol Chem*, 1933, ci, 93-104
- 6 GUTMAN, A B, OLSON, K B, GUTMAN, E B, and FLOOD, C A Effect of disease of liver and biliary tract upon phosphatase activity of serum, *Jr Clin Invest*, 1940, xix, 129-152
- 7 QUICK, A J Clinical application of hippuric acid and prothrombin tests, *Am Jr Clin Path*, 1940, x, 222-233
- 8 QUICK, A J OTTENSTEIN, H N, and WELTCHER, H Synthesis of hippuric acid in man following intravenous injection of sodium benzoate, *Proc Soc Exper Biol and Med*, 1938, xxxviii, 77-78
- 9 WEICHELBAUM, T E, and PROBSTEN, J G Determination of hippuric acid in urine, *Jr Lab and Clin Med*, 1939, xxiv, 636-639
- 10 ROSENTHAL, S M, and WHITE, E C Clinical application of bromsulphalein test for hepatic function, *Jr Am Med Assoc*, 1925, lxxxiv, 1112-1114
- 11 O'LEARY, P A, GREENE, C H, and ROWNTREE, L G Diseases of liver, various types of syphilis of liver with reference to tests for hepatic function, *Arch Int Med*, 1929, xlv, 155-193
- SNELL, A M, and MAGATH, T B Use and interpretation of tests for liver function, clinical review, *Jr Am Med Assoc*, 1938, cx, 167-174
- 12 MATEER, J G, BALTZ, J I, MARION, D F, and HOLLAND, R A unpublished data
- 13 DE LOR, C J, and REINHART, H L Analysis of hippuric acid, galactose tolerance, bromsulphalein and prothrombin tests in 381 cases, *Am Jr Clin Path*, 1940, x, 617-622
- 14 BEST, C H, and TAYLOR, N B The physiological basis of medical practice, 2nd edition, 1939, Williams and Wilkins Co, Baltimore
- 15 HAINES, S F, MAGATH, T B, and POWER, M H Hippuric acid test in hyperthyroidism, *Proc Staff Meet Mayo Clin*, 1939, xiv, 495-496

SOME EFFECTS OF POTASSIUM SALTS IN MAN^{*}

By NORMAN M. KEIHL, M.D., ARNOLD E. OSTERBERG, Ph.D., and
HOWARD B. BURCHELL, M.D., *Rochester, Minnesota*

DURING the last few years both the physiologist and the clinician have discovered many new facts regarding the metabolism of potassium. Several factors have stimulated recent studies in this subject and among these have been the availability of accurate microchemical methods for the estimation of potassium in body fluids, the application of physiologic principles to the study of certain clinical syndromes and a desire to establish more clearly the dividing line between the pharmacologic and toxic effects of potassium salts.

The problem of toxicity has been confused in the past by conflicting results obtained in two types of studies. The initial experiments of Blake¹ in 1839 revealed that the rapid intravenous injection of a potassium salt into a dog is quickly fatal. However, 40 years later, in 1881, Feltz and Ritter² injected a similar dose slowly, for example in 10 minutes, and no untoward symptoms developed. The latter result gave us a clue as to why relatively large doses of potassium salts have been given by mouth for many years without obvious toxic effects. As much as 40 gm. of potassium chloride have been ingested in one day by patients suffering from myasthenia gravis without toxic symptoms.³ McQuarrie and coworkers⁴ reported the administration by mouth of 48 gm. of the same salt daily to a patient who had acromegaly and hypoglycemia, no untoward effects occurred. Apparently osmotic and other factors acting within the lumen of the small bowel prevent too rapid absorption of potassium salts into the blood stream. The experiments of Winkler, Hoff and Smith⁵ in the dog support such a point of view. Therefore, to ascertain the single maximal nontoxic dose of a potassium salt given by mouth to a human subject seemed to be a pharmacologic problem worthy of further study. We shall proceed to outline such an attempt in which normal volunteers were subjects and endeavor to follow the lead so ably given by Ringer and Murrell⁶ in 1878 in their well-known experiments in the frog. Ringer interpreted their results as revealing that potassium salts in large doses had a toxic effect on the nervous and muscular tissues, but emphasized that they had a widespread toxic action on all "nitrogenous tissue."

EFFECT OF POTASSIUM ON THE KIDNEY

Our first objective was to determine the effect of a large single dose of a potassium salt on the renal clearance of potassium and inulin. Seven normal persons ingested 12.5 to 17.5 gm. of potassium chloride or bicarbonate and

^{*} Read before the ninety-second annual session of the American Medical Association, Section on Pharmacology and Therapeutics, Cleveland, Ohio, June 5, 1941.

Received for publication August 6, 1941

after absorption had occurred the clearances were estimated * The routine procedure in these studies consisted in obtaining a control specimen of urine in the early morning, the ingestion of a given potassium salt in 6 to 25 per cent solutions, and then collection of hourly or half hourly specimens of urine No food was taken in four studies, but to prevent epigastric burning in three a small breakfast was eaten just before ingestion of the potassium salt This consisted of either two soft boiled eggs or a small portion of oat porridge and 50 c c milk In order to have a satisfactory volume of urine for clearance studies 100 to 200 c c of water were ingested every half to one hour throughout the observations The inulin clearance was determined after the intravenous injection of 100 c c of a 10 per cent solution of inulin containing 0.9 per cent sodium chloride, and the chemical determinations in the blood and urine were made according to Alving's ^{7,8} method

In five subjects the potassium clearance rose from the normal fasting level of 6 to 14 c c ^{9,10} to 41 to 105 c c, but that of inulin was within the normal range, 93 to 146 c c (table 1) During the clearance periods the concentration of potassium in the serum varied from 22 to 28 mg per 100 c c Similar

TABLE I
Renal Clearances Large Single Dose of Potassium Salt without Toxic Action

Subject (normal person) and surface area, sq m	Dose, gm		Experimental period, minutes	Urine minute volume, c c	Plasma and serum clearance*			
	Potassium salt	Potassium†			Inulin	Potassium	Urea	Ratio of potassium to inulin
K ₁ 1.97	12.5 KHCO ₃	4.9	30	3.5	115	52		0.45
	9.5 KCl‡	5.0	67	2.6	143	58	67	0.41
Bu 1.75	12.5 KHCO ₃	4.9	31	14.8	137	105		0.77
Ke 1.95	17.5 KHCO ₃	6.8	30	2.8	134	41		0.31
Gr 1.92	17.5 KHCO ₃	6.8	30	3.2	93	49		0.53
			30	2.9	115	44		0.38
Ro 1.74	12.5 KCl	6.5	30	4.1	146	49	77	0.34
Mean					126	57		0.46

* Calculated as c c per 1.73 sq m per minute

† 0.06-0.1 gm per kilogram of body weight

‡ Injected intravenously in ninety minutes

* The potassium in the serum was determined by the method of Kramer, Benjamin and Tisdall, F F A clinical method for the quantitative determination of potassium in small amounts of serum, Jr Biol Chem, 1921, xlv, 339-349 This method in our hands has been checked with gravimetric procedures The precipitation by sodium cobalt-nitrite was allowed to proceed for 45 minutes at icebox temperature in order to obtain a good granular precipitate If this and other steps are adhered to rigorously, the method is a satisfactory procedure Potassium in urine was estimated by this method after ashing

doses of the same salts, however, administered to two additional normal persons, caused the potassium clearance to rise to 37 and 64 c c, and the concentration of potassium in the serum to 19 to 33 mg per 100 c c, but at the same time caused a fall in both the inulin and the urea clearance¹¹ to less than the normal levels. The minimal values for inulin were 71 and 77 c c and for urea 50 and 47 c c in these two subjects (table 2). Therefore, in

TABLE II
Renal Clearances: Large Single Dose of Potassium Salt with Toxic (?) Action

Subject (normal person) and surface area sq. m.	Dose gm.		Experimental period minutes	Urine minute volume c.c.	Plasma and serum clearances*			
	Potassium salt	Potassium†			Inulin	Potassium	Urea	Ratio of potassium to inulin
F1 1.80	Control	6.8	30	13.8	107	7	99	0.07
			30	10.3	119		76	
	17.5 KHCO ₃		30	3.6	71	64	50	0.90
	30		3.8	72	50		0.69	
W1 1.98	Control	6.5	30	10.7	143	10	70	0.07
			30	8.7	145	9	65	0.06
	12.5 KCl		30	9.1	77	37	64	0.48
	35		2.7	80	36	47	0.45	

* Calculated as c c per 1.73 sq. m. per minute

† 0.08-0.1 gm. per kilogram of body weight

two subjects the large dose of potassium disturbed normal renal excretion. The decreased inulin clearance indicates reduced glomerular filtration. The results of all seven studies reveal that a single dose of a potassium salt containing 80 to 100 mg of potassium per kilogram of body weight may or may not have a toxic action on the kidney. Obviously such a dose is close to the toxic level for the normal kidney.

Considerable evidence has accumulated that the diseased kidney often can excrete potassium salts satisfactorily^{12, 5}. This has been particularly true in cases of chronic glomerulonephritis with edema in which these salts have produced a diuretic action¹². On the other hand, we now know that it is dangerous to give potassium salts in cases of nephritis in which severe renal insufficiency is present. Caution in their use is especially indicated in cases of severe acute renal failure, of severe passive congestion of the kidney^{13, 14, 15} and during the terminal phase of uremia¹⁵.

EFFECT OF POTASSIUM ON SENSORY NERVE ENDINGS

Because of a certain amount of discomfort in the epigastrium after the ingestion of these large doses of potassium salts it seemed expedient to study

the effect of a potassium salt on renal function after intravenous injection. Such an attempt was made on two healthy volunteers. At the onset of the intravenous injection of 1 per cent solution of potassium chloride both subjects complained of severe burning pain extending from the site of injection in the elbow vein up and along the arm vein to the shoulder. The site and type of pain were apparently similar to those experienced after the rapid intravenous injection of 10 per cent solutions of calcium and magnesium chloride. Further attempts in several other veins also were attended by pain in one volunteer, but the second volunteer managed to take slowly, over a period of 91 minutes, 950 cc of the 1 per cent solution of potassium chloride without pain. The concentration of potassium in the serum rose from the control value of 18.3 to 22 mg per 100 cc and the clearance to 58 cc, but the clearances of inulin and urea were normal, 143 and 67 cc respectively (subject K₁ [normal person], table 1). Therefore, this injection did not have any demonstrable toxic effects on the function of the kidney but confirmed the findings of others that a too rapid intravenous injection of a solution of potassium salts gives rise to severe pain along the vein into which the injection is made. Pudenz and his co-workers¹⁶ reported that their patient suffering from periodic familial paralysis, during an attack of paralysis, when the concentration of potassium in the serum was decidedly low, was given intravenous injections of a 0.5 to 2.0 per cent solution of potassium chloride, a total of 10 gm in 10 minutes, the patient complained of such severe burning pain along the vein that on one occasion he stated that he would rather remain paralyzed than submit to such an injection.

The localization of this pain along the veins into which the injection was made naturally suggested that sensory nerve endings for pain in these vessels had been stimulated by the potassium solution. Moore and his co-workers^{17, 18} showed experimentally in the cat that intra-arterial injections of potassium salts stimulate the nerve endings for pain in these arteries. Moore also observed, however, that intravenous injections in these animals had no such effect. The investigations of Habler and Hummel¹⁹ in 1928 revealed that in human subjects intracutaneous injection of isotonic solutions of potassium salts always caused pain within 20 seconds whereas isotonic solutions of similar sodium salts did not cause pain. These facts with regard to the possible stimulation of sensory nerve endings for pain in different tissues by potassium salts offered us a possible explanation of a certain untoward symptom described by Arden²⁰ after the ingestion by mouth of 150 gm of potassium chloride or potassium bicarbonate. Arden described the development of paresthesia in the hands and feet some 40 minutes after the salt had been taken and its subsequent persistence for three to four hours. Could this paresthesia in the hands and feet be related to an increase in the concentration of potassium in the serum, which in turn stimulated peripheral nerve endings?

In one of our observations the volunteer ingested 12.5 gm of potassium chloride and while we were studying his potassium and inulin clearances he

complained of paresthesia in his hands and feet. This subject was one of the two volunteers, mentioned already, in whom low inulin and urea clearances developed (subject W₁ [normal person], tables 2 and 3, figure 1). This lat-

TABLE III

Serum Potassium and Paresthesia of Hands and Feet * Large Single Dose of Potassium Salt; Subject W₁ (Normal Person)

Dose gm		Serum potassium mg in 100 cc	Inulin clearance†	Paresthesia of hands and feet grade
Potassium salt	Potassium†			
12.5 KCl	6.5	33.2	77	3

* Two to three hours after ingestion of salt

† 0.08 gm. per kilogram of body weight

‡ Calculated as cc per 1.73 sq. m. per minute

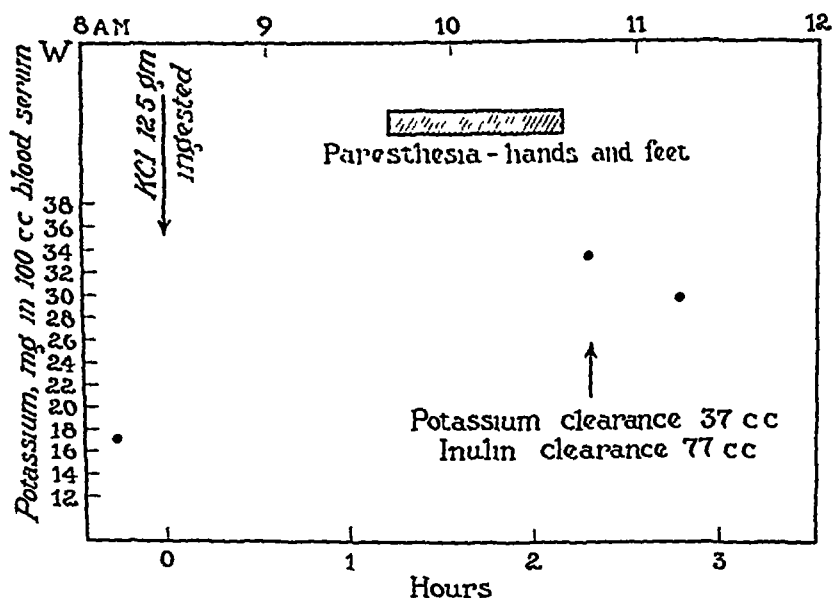


FIG 1 Subject W₁ (normal person, tables 2 and 3) Concomitant development of paresthesia in hands and feet with a rise in concentration of potassium to 33.2 mg per 100 cc of serum and a reduction of inulin clearance to 77 cc

ter finding suggested a possible toxic effect on the kidney while the presence of paresthesia suggested a toxic effect on the sensory nerve endings in the peripheral tissues of the hands and feet. It was noted also that at the time the clearances were estimated and the paresthesia was felt, the concentration of potassium in the serum had increased to 33.2 mg per 100 cc. In a similar study of another volunteer we have since observed the development of paresthesia in the hands and feet accompanied by a concentration of potassium in the serum of 32.8 mg per 100 cc (subject Ke [normal person], figure 2). In a third study, a patient suffering from diffuse cardiovascular disease and hypertension consented to take the same dose of potassium

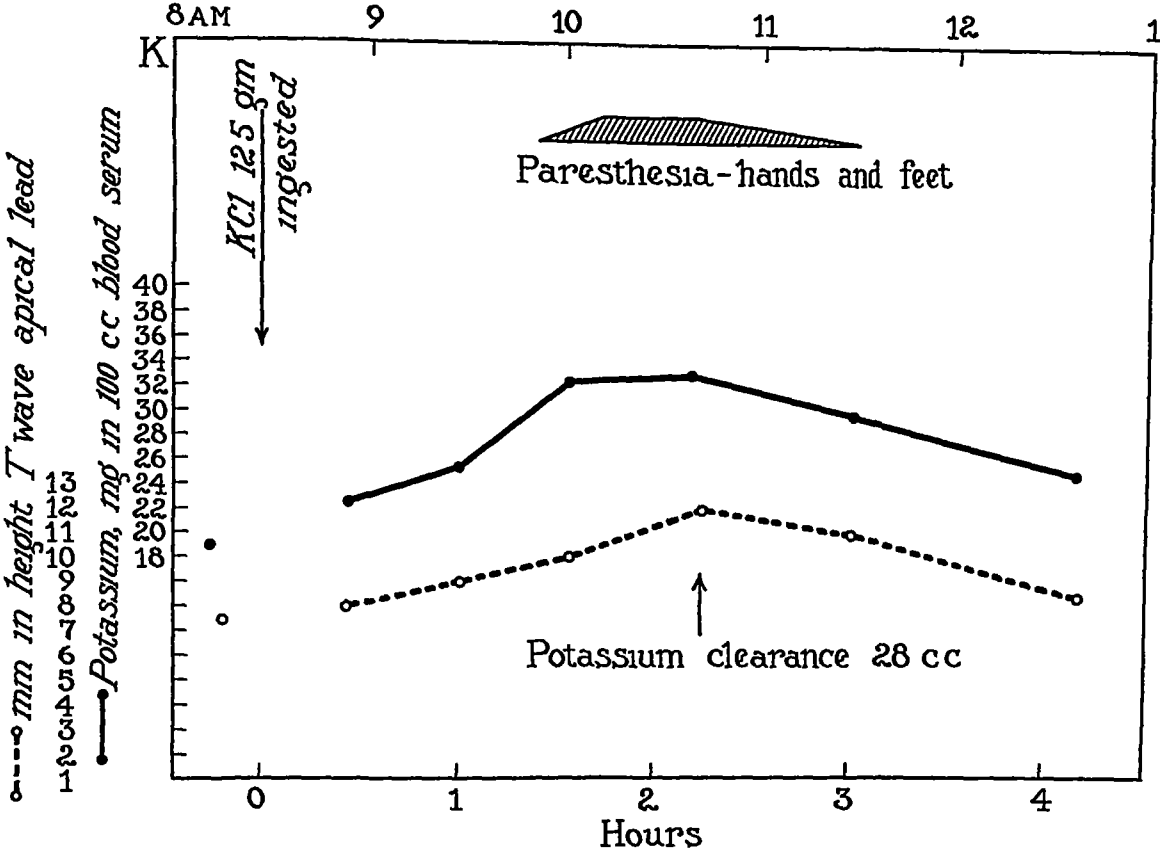


FIG 2 Subject Ke (normal person, tables 1 and 4) Concomitant development of paresthesia in hands and feet with a rise in concentration of potassium to 32.8 mg per 100 cc of serum and a rise of 4.5 mm in the T-wave of the electrocardiogram

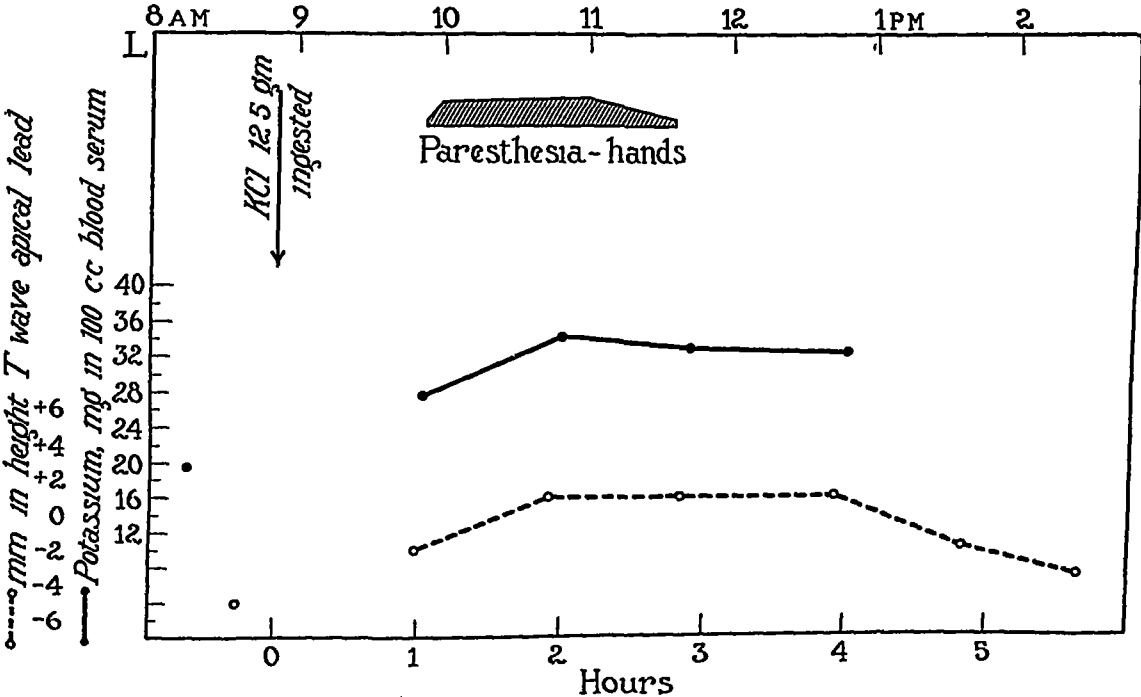


FIG 3 Subject La (patient, table 4) Simultaneous occurrence of paresthesia in hands with a rise in concentration of potassium to 34.2 mg per 100 cc of serum and a rise of 6.0 mm in the T-wave of the electrocardiogram. Note also slow fall of both serum potassium and T-wave

chlouide. Paresthesia developed in his hands but not in his feet when the concentration of potassium rose to 34.2 mg per 100 cc of serum (subject La [patient], figure 3). On the other hand, a normal volunteer ingested the same amount of potassium chloride but paresthesia did not develop nor did the concentration of potassium rise to more than 26.3 mg per 100 cc of serum. However, he excreted potassium rapidly in the urine, the clearance amounting to 95 cc (subject Bu [normal person], figure 4).⁴ Noin²¹ in 1929 re-

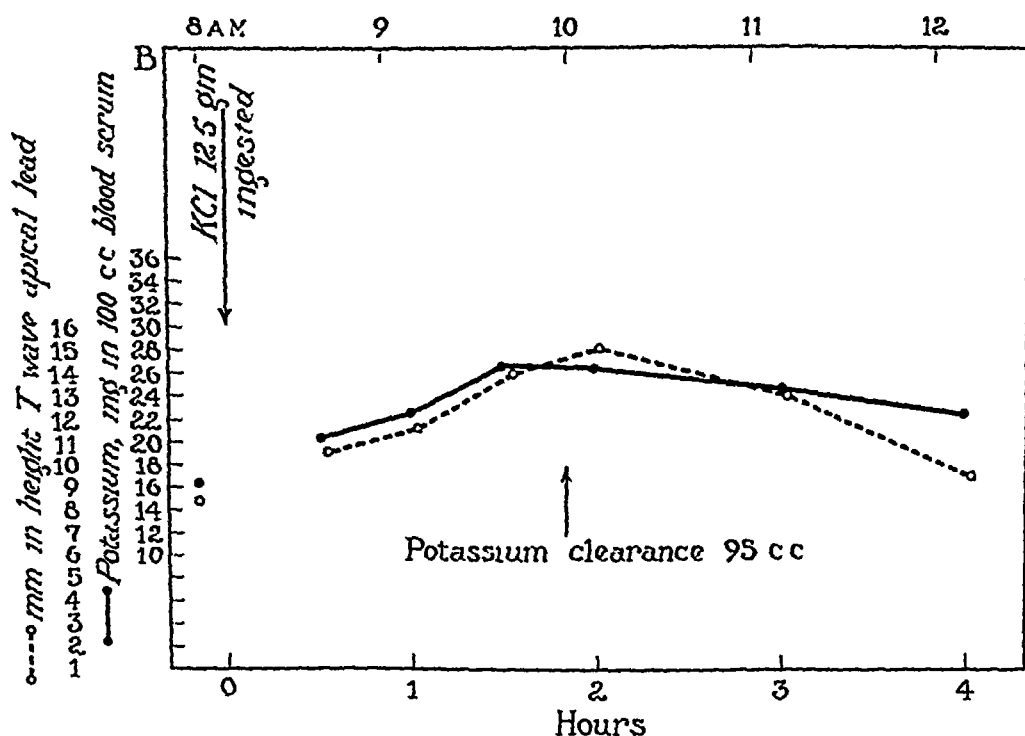


FIG 4 Subject Bu (normal person, tables 1 and 4). Simultaneous occurrence of a rise in concentration of potassium to 26.3 mg per 100 cc of serum, a rise of 6.5 mm in the T-wave of the electrocardiogram and a potassium clearance of 95 cc.

ported a similar experience to subject Bu in which paresthesia did not occur. This type of study suggests that there is a close relation between a rapid rise in the concentration of potassium from normal values to 30 mg per 100 cc of serum, and development of peripheral paresthesia.

EFFECT OF POTASSIUM ON THE HEART

Blake, in 1839, and subsequent investigators have suggested that death which followed a rapid intravenous injection of a potassium salt into an animal was due to the sudden cessation of the movements of the heart. Potassium appears to have a dual toxic action on the heart, affecting both the conduction system and the muscle of the heart. Winkler, Hoff and Smith²²

* This subject's intake of water and output of urine were high in both this and a previous study (table 1). The large intake of water may have played an important rôle in the resulting high potassium clearances, however, in other persons a large volume of urine was accompanied by a much lower potassium clearance.

have demonstrated in their recent experiments the progressive changes that develop in a series of electrocardiograms taken as the toxic action on the animal's heart increases. Similar changes have also been demonstrated in the cat by Chamberlain, Scudder and Zwemei^{22a}. Their results confirm the earlier observations of Wiggers²³ in dogs that potassium salts cause a rise in the T-wave of the electrocardiogram early and before auricular or ventricular fibrillation sets in. McLean, Bay and Hastings²⁴ perfused isolated hearts of rabbits with a fluid containing various concentrations of potassium chloride and demonstrated that increasing the concentration of potassium to 35.3 mg per 100 c.c. caused a marked rise in the T-wave whereas decreasing it to 11.8 mg per 100 c.c. had the reverse effect.

There is increasing evidence that similar changes in the T-wave of the electrocardiogram can occur in man. For example, after a normal person has ingested a large dose of a potassium salt a rise in the T-wave can be demonstrated. There are also patients who have certain clinical conditions in which the concentration of potassium in the serum may be increased or decreased abnormally and who show a corresponding rise or fall in the T-wave. Thomson²⁵ in 1939 demonstrated in examination of a patient who had Addison's disease that a high concentration of potassium in the serum was associated with an increased T-wave in the electrocardiogram. He subsequently showed a similar relation in patients who had cardiac disease and who were ingesting considerable amounts of potassium salts²⁶.

In order to follow Thomson's studies further, two normal subjects and a patient who had diffuse cardiovascular disease and hypertension²⁷ consented to take 12.5 gm potassium chloride, in a single dose. It is of interest that an electrocardiographic tracing of this patient taken during a control period showed inversion of the T-waves in Leads I and IV. Before and at periodic intervals after the ingestion of the salt, electrocardiographic tracings of the three volunteers were taken and estimations of the concentration of

TABLE IV

Serum Potassium and T-Wave in Electrocardiogram * Large Single Dose of Potassium Salt

Subject (normal person or patient)	Dose gm		Serum potassium, mg in 100 c.c.	Electrocardiogram rise in T-wave, mm ‡
	Potassium salt	Potassium†		
Ke	12.5 KCl	6.5	32.8	4.5
La §	12.5 KCl	6.5	34.2	6.0
Bu	12.5 KCl	6.5	26.3	6.5

* Two to three hours after ingestion of potassium salt

† 0.069 to 0.104 gm per kilogram of body weight

‡ T-wave in apical lead

§ Patient had diffuse cardiovascular disease with hypertension

potassium in the serum were made*. Both the concentration of potassium in the serum and the T-waves in the electrocardiograms showed in all three studies a steady rise until they reached a maximum in approximately two hours (table 4, figures 2, 3, 4, 5 and 6). In the two normal volunteers

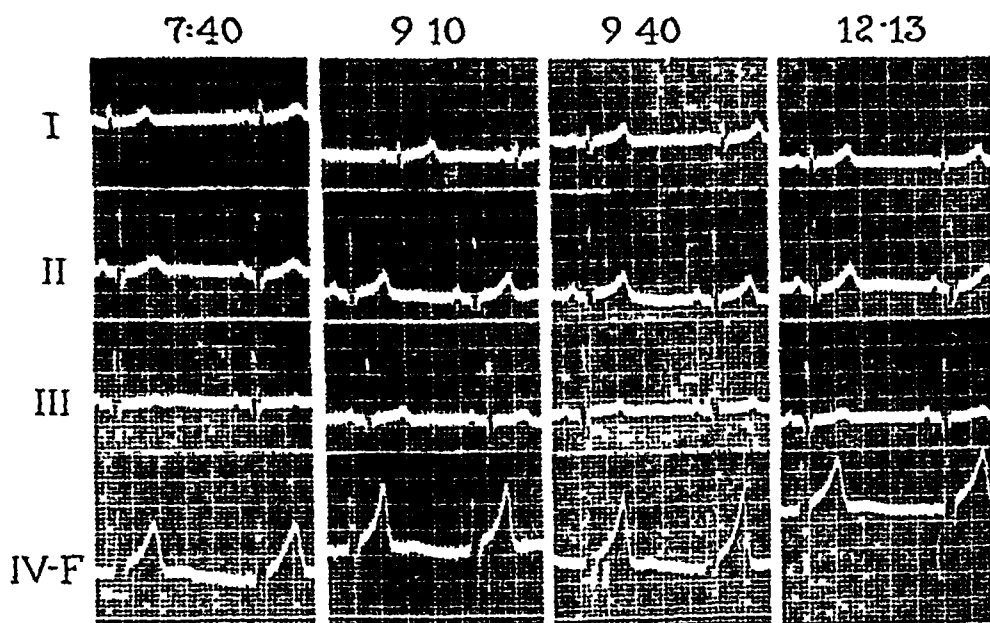


FIG 5 Subject Bu (normal person, tables 1 and 4) Changes in the T-wave of the electrocardiogram of a normal person after ingestion of 12.5 gm potassium chloride at 8:08 a.m.

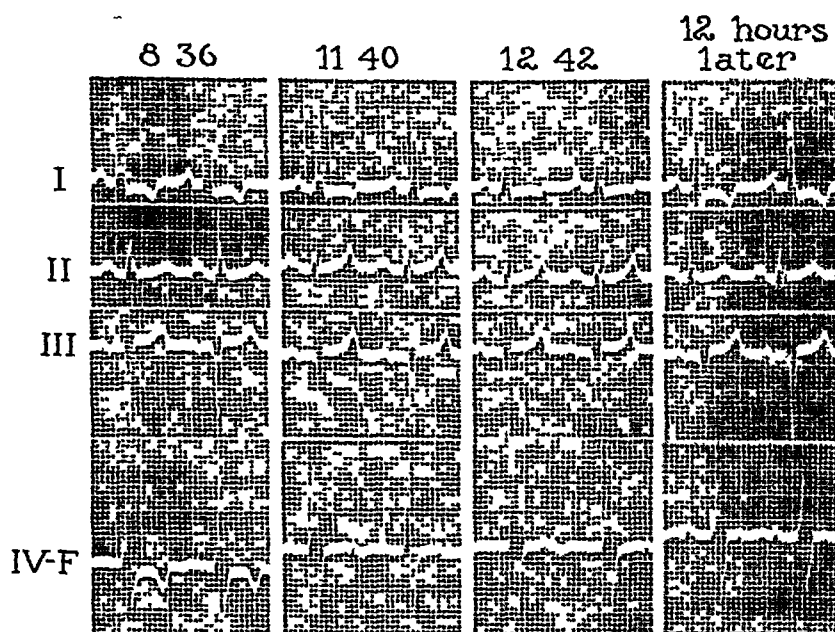


FIG 6 Subject La (patient, table 4) Changes in the T-wave of the electrocardiogram of a patient suffering from diffuse cardiovascular disease and hypertension after ingestion of 12.5 gm potassium chloride at 8:49 a.m.

* The pulse rate was estimated periodically and no marked changes from the normal control rate were observed. Blood pressure readings were not taken during these studies.

there was a gradual decline in the serum potassium and in the T-waves until control levels were approached in four to six hours. However, in the patient who had vascular disease (subject La) the decline in concentration of potassium in the serum was much slower and even after 12 hours the T-waves had not receded to the control level (figures 3 and 6). It also should be pointed out that in the normal subject Bu the T-waves rose the highest but the rise in serum potassium was the least (table 4, figure 4). This observation is in agreement with Thomson's findings in patients, that usually the increase in the T-wave was associated with a rise in the concentration of potassium in the serum, but this relationship varied and was not a constant one.

Janota and Weber²⁸ in 1928 obtained an electrocardiogram in examination of a patient suffering from familial periodic paralysis during a paralytic episode and observed a distinct lowering of the T-wave. With recovery from the paralysis the electrocardiogram became normal. A similar finding was reported later by Zabriskie and Frantz²⁹. Several investigators beginning with Aitken, Allott, Castleden and Walker³⁰ in 1937 have made the interesting observation that during the paralytic attack in such a patient the concentration of potassium in the serum is markedly reduced and that with recovery it rises to normal. Stoll and Nisnewitz³¹ early in 1941 made both an electrocardiographic tracing and a serum potassium estimation during an attack of paralysis in one of these patients. As was to be expected, both the serum potassium and the T-waves were reduced definitely.

SIMULTANEOUS DIFFUSE EFFECTS OF POTASSIUM

It is quite clear from the foregoing studies that potassium salts after absorption into the blood stream may exert widespread effects throughout the body. Several simultaneous actions in different organs of subjects W₁, Ke, Bu (normal persons) and La (patient) are depicted graphically in figures 1, 2, 3 and 4. In subject W₁ (normal person, figure 1) paresthesia in the hands and feet and reduced renal clearances of inulin and urea occurred at a time when the concentration of potassium in the blood stream had risen to 33.2 mg per 100 c.c. of serum. Apparently at this high concentration of potassium in the serum, the ability of the kidney to excrete inulin and urea was reduced, and the nerve endings in the skin of the hands and feet were stimulated abnormally. In subject Ke (normal person, figure 2), in addition to the high concentration of potassium of 32.8 mg per 100 c.c. of serum and the presence of paresthesia in the hands and feet, there is a distinct rise of 4.5 mm in the T-wave of the electrocardiogram. In this subject we learn that with a similar high concentration of potassium in the serum, as observed in the previous study, abnormal peripheral sensory disturbances occur at the same time as the T-waves in the heart are altered. In subject La (patient, figure 3) the results are similar to those in the previous subject Ke (normal person). It is of interest, however, that the T-waves were abnormally low in the electrocardiogram taken previous to the ingestion of potassium and

that the low T-waves were increased distinctly when the concentration of potassium in the serum became distinctly high

The application of certain technical procedures in these four studies has shown that scattered abnormal functional disturbances sometimes can be correlated with an abnormal symptom, and further that if paresthesia in the hands or feet, or in both, develops after the ingestion of a potassium salt, it is fairly safe to conclude that the concentration of potassium has increased to 30 mg per 100 c c of serum and that T-wave changes can be demonstrated in the electrocardiogram

COMMENT

Certain practical considerations emerge from the facts presented in this study. First of all we have learned that protective mechanisms are called into play when too large doses of potassium salts are injected intravenously or ingested by mouth. The stimulation of pain along the vein into which the solution is injected protects the organism from too rapid an entry of potassium into the vascular system and tissue spaces. Likewise after the ingestion and absorption of a considerable dose of potassium the onset of paresthesia in the hands and feet should warn us that the concentration of potassium in the serum has risen quickly to a level which may cause diffuse toxic effects. In a similar manner T-wave changes in the electrocardiogram may be a danger signal, although from present knowledge it is quite clear that their presence alone does not indicate significant dysfunction of the heart. Another practical point is that there are definite indications that in both severe adrenal and renal insufficiency the tissues have a reduced tolerance for potassium salts. This may also apply to patients who have diabetes mellitus.⁴ This fact seems true both after experimental adrenalectomy^{32, 33} and in patients who have Addison's disease.³⁴ The problem is not so clear with regard to renal insufficiency. In some abnormal renal states there is greater intolerance than in others to potassium salts. The closer the renal insufficiency is to total loss of renal function in either experimental or clinical conditions,^{35, 36, 37, 38} the more likely it seems that there will be intolerance to potassium. However, in moderate renal insufficiency patients often tolerate it well. From these practical considerations one finally concludes that there is considerable individual variation as to what constitutes a toxic dose of a potassium salt, that potassium salts can be given safely in considerable doses in a variety of disease conditions, and that the method of administering moderate repeated doses is safer than giving a large single one.

The fundamental action of potassium salts is related intimately to cellular function* in various tissues. This applies to muscular activity whether in voluntary muscle or the myocardium. Numerous investigators so far have failed to explain adequately the mechanism of potassium in muscular physiology. Some have thought that it was associated intimately with reactions in

*The term "cellular function" refers to both the membrane enclosing the cell and the intracellular protoplasm.

the myoneural junctions, others that its rôle was linked closely with action of hormones such as epinephrine, insulin and cortin within the muscle cell³⁹ The beneficial action of potassium salts in familial periodic paralysis and in myasthenia gravis suggests a neuromuscular effect

A discussion of the diuretic action of potassium salts is of some theoretical interest Normally after 12 hours of fasting the renal clearance of potassium is remarkably small when compared with that of inulin,^{9, 10, 5} the potassium-inulin clearance ratio averages 0.10 This ratio would seem to indicate that a large percentage of the potassium filtered by the glomeruli is reabsorbed by the tubules With large doses of potassium salts the potassium-inulin clearance ratio rises, in six of our studies on normal persons, the ratio rose to from 0.31 to 0.77 This variable increase in potassium clearance occurred when there was only a moderate increase in the concentration of potassium in the serum, actually from 22 to 28 mg per 100 c.c. This rise in concentration of potassium in the serum presumably also occurred in the glomerular ultrafiltrate If from these data one computes the possible reabsorption and excretion of potassium by the tubules, it will be seen that when the potassium-inulin clearance ratio is between 0.31 and 0.45 the absolute amount of potassium reabsorbed is always greater than that excreted In the one case in which the potassium-inulin ratio reached 0.77, the amount excreted exceeded greatly the amount reabsorbed The implication of these calculations would seem to be that increased excretion of potassium by the kidney is not always due simply to a rejection of potassium by the tubular cells but is the result of a variable alteration in the balance between reabsorption and excretion in these cells The diuretic action of potassium salts would appear, therefore, to be the result of a temporary change in the cellular function of the cells of the renal tubules

The results reported in this paper reveal that the effects of potassium are widespread throughout the body and are in all probability dependent on altered cellular activity Further knowledge regarding the potassium problem is dependent on the continuance of similar studies as well as on an increased understanding of fundamental cellular physiology

SUMMARY

A considerable amount of several potassium salts may be ingested by the normal person without demonstrable toxic effects Similar doses may be given with safety to patients suffering from various diseases, but their use is specifically contraindicated in cases of severe renal and adrenal insufficiency An important symptom, indicative of toxic action, is the development of paresthesia in the hands and feet It is accompanied by a rapid rise in the concentration of potassium in blood serum to approximately 30 mg per 100 c.c. The diffuse action of potassium is revealed by the simultaneous production of effects on the functions of the heart, kidney and peripheral nerve endings

REFERENCES

- 1 BLAKE, I Observations on the physiological effects of various agents introduced into the circulation as indicated by the haemodynamometer, *Edinburgh Med Jr*, 1839, li, 330-345
- 2 ELTZ, V, and RITZER, E *Le larcime experimentale*, 1881, Berger-Levrault et Cie, Paris
- 3 GALLOTT, I H, and SCHWAB R S Recent advances in the biochemistry and therapeutics of potassium salts, *New England Jr Med* 1940, ccxvii, 585-590
- 4 MCQUARRIE, IRVINE, THOMPSON W H, and ANDERSON, J A Effects of excessive ingestion of sodium and potassium salts on carbohydrate metabolism and blood pressure in diabetic children, *Jr Nutr*, 1936, vi, 77-101
- 5 WINKLER, A W, HOFF, H E, and SMITH P K The toxicity of orally administered potassium salts in renal insufficiency, *Jr Clin Invest* 1941, xx, 119-126
- 6 RINGER, SYDNEY and MURRELL W Concerning the effects on frogs of arrest of the circulation, and an explanation of the action of potash salts on the animal body, *Jr Physiol*, 1878-1879 i, 72-95
- 7 ALVING, A S, RUBIN, JACK, and MILLER, B F A direct colorimetric method for the determination of inulin in blood and urine, *Jr Biol Chem*, 1939 cxvii, 609-616
- 8 MILLER, B F ALVING, A S, and RUBIN, JACK The renal excretion of inulin at low plasma concentrations of this compound, and its relationship to the glomerular filtration rate in normal nephritic and hypertensive individuals, *Jr Clin Invest*, 1940, xix, 89-94
- 9 KEITH, N M, and OSTERBERG, A E The excretion of potassium by the kidney, *Am Jr Physiol*, 1940, cxviii, 395-396
- 10 KEITH, N M, OSTERBERG, A E, and KING, H E The excretion of potassium by the normal and diseased kidney, *Trans Assoc Am Phys*, 1940, li, 219-221
- 11 VAN SLAKE, D D and CULLEN, G E A permanent preparation of urease, and its use in the determination of urea *Jr Biol Chem*, 1914, xix, 211-228
- 12 KEITH, N M, and BINGER, M W Diuretic action of potassium salts, *Jr Am Med Assoc*, 1935, cx, 1584-1590
- 13 OLMER, D, PAVAN, L, and BERTHIER, J Le potassium du serum sanguin dans l'insuffisance rénale, *Compt rend Soc de biol*, 1922, lxxvii, 867-869
- 14 SCHOLTZ, H G Über den Calcium- und Kaliumgehalt im Blutserum und die Ultrafiltrierbarkeit dieser Minerale bei Niereninsuffizienz, *Deutsch Arch f klin Med*, 1932, clxxii, 472-482
- 15 KEITH, N M, KING, H E, and OSTERBERG, A E The serum concentration and renal clearance of potassium in severe renal insufficiency, *Federation Proceedings*, 1942, pt 2, i, 180
- 16 PUDENZ, R H, MCINTOSH, J F, and MCEACHERN, DONALD The rôle of potassium in familial periodic paralysis, *Jr Am Med Assoc*, 1938, cx, 2253-2258
- 17 MOORE, R M, MOORE, R E, and SINGLETON, A O, JR Experiments on the chemical stimulation of pain-endings associated with small blood-vessels, *Am Jr Physiol*, 1934 cvii, 594-602
- 18 MOORE, R M The stimulation of peripheral nerve-elements subserving pain-sensibility by intra-arterial injections of neutral solutions, *Am Jr Physiol*, 1934, cx, 191-197
- 19 HABLER, C, and HUMMEL, R Über die schmerzauslösende Wirkung des K-ions, *Klin Wchnschr*, 1928, vii, 2151-2153
- 20 ARDEN, FELIX Experimental observations upon thirst and on potassium overdosage, *Australian Jr Exper Biol and Med Sci*, 1934, vii, 121-122
- 21 NORN, MOGENS Untersuchungen über das Verhalten des Kaliums im Organismus III Über Schwankungen der Kaliumkonzentration des Plasmas nach Eingabe von Kaliumsalzen und bei verschiedenen Diureseformen und ihre Beziehung zur Kaliumausscheidung im Harn, *Skand Arch f Physiol*, 1929, lv, 211-229

- 22 WINKLER, A W, HOFF, H E, and SMITH, P K Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride, *Am Jr Physiol*, 1938, cxxiv, 478-483
- 22a CHAMBERLAIN, F L, SCUDDER, J, and ZWEMER, R L Electrocardiographic changes associated with experimental alterations in blood potassium in cats, *Am Heart Jr*, 1939, xviii, 458-470
- 23 WIGGERS, C J Studies on ventricular fibrillation produced by electric shock III The action of antagonistic salts, *Am Jr Physiol*, 1930, xciii, 197-212
- 24 MCLEAN, F C, BAY, E B, and HASTINGS, A B Electrical changes in the isolated heart of the rabbit following changes in the potassium content of the perfusing fluid, *Am Jr Physiol*, 1933, cv, 72-73
- 25 THOMSON, W A R Potassium and the T-wave of the electrocardiogram, *Lancet*, 1939, i, 808-811
- 26 THOMSON, W A R The effect of potassium on the heart in man, *Brit Heart Jr*, 1939, i, 269-282
- 27 KEITH, N M, OSTERBERG, A E, and BURCHELL, H B Some effects of potassium salts in man, *Jr Pharmacol and Exper Therap*, 1941, lxxxii, 22-23
- 28 JANOTA, OTAKAR, and WEBER, KLEMENT Die paroxysmale Lahmung, eine Studie ueber ihre Klinik und Pathogenese, *Abhandl a d Neurol, Psychiat, Psychol u Grenzgeb*, 1928, xlv, 1-118
- 29 ZABRISKIE, E G, and FRANTZ, A M Familial periodic paralysis, *Bull Neurol Inst New York*, 1932, ii, 57-74
- 30 AITKEN, R S, ALLOTT, E N, CASTLEDEN, L I M, and WALKER, MARY Observations on a case of familial periodic paralysis, *Clin Sci*, 1937, iii, 47-57
- 31 STOLL, BERNARD, and NISNEWITZ, SAMUEL Electrocardiographic studies in a case of periodic paralysis, *Arch Int Med*, 1941, lxxvii, 755-761
- 32 KENDALL, E C, MASON, H L, MYERS, C S, and ALLERS, W D A physiologic and chemical investigation of the suprarenal cortex, *Jr Biol Chem*, 1936, cxiv, 57-58
- 33 WINKLER, A W, HOFF, H E, and SMITH, P K Toxicity of potassium in adrenalectomized dogs, *Am Jr Physiol*, 1941, cxxxiii, 494-495
- 34 WILDER, R M, KENDALL, E C, SNELL, A M, KEPLER, E J, RYNEARSON, E H, and ADAMS, MILDRED Intake of potassium, an important consideration in Addison's disease, a metabolic study, *Arch Int Med*, 1937, lxx, 367-393
- 35 SMILLIE, W G Potassium poisoning in nephritis, *Arch Int Med*, 1915, xvi, 330-339
- 36 ADDIS, T, and LEW, W Diet and death in acute uremia, *Jr Clin Invest*, 1939, xviii, 773-775
- 37 BERGMAN, H C, and DRURY, D R A study of acute renal insufficiency, *Jr Clin Invest*, 1939, xviii, 777-781
- 38 HOFF, H E, SMITH, P K, and WINKLER, A W The cause of death in experimental anuria, *Am Jr Physiol*, 1941, cxxxiii, 331-332
- 39 FLANN, W O The rôle of potassium in physiological processes, *Physiol Rev*, 1940, xx, 377-415

**TREATMENT OF DIABETES MELLITUS WITH
PROTAMINE INSULIN: IS A PERSISTENT
GLYCOSURIA HARMFUL? A ME-
TABOLIC STUDY OF A
SEVERE CASE"**

By EDWARD TOLSON, M D, THOMAS P ALMY, M D, and VINCENT
TOSCANI, B S, *New York, N Y*

Two years ago, we presented our criteria for the satisfactory treatment of diabetes mellitus with protamine insulin. Briefly, we preferred (a) one injection a day, and (b) we were guided by the patient's weight, (c) his freedom from symptoms, (d) his freedom from ketonuria, and (e) the absence of insulin reactions. The experimental and clinical evidence upon which this treatment was based has been published in detail elsewhere¹. It was our experience that the most reliable protection the patient had from the hypoglycemic syndrome was a glycosuria. We, therefore, included among our criteria the desirability of a glycosuria.

Our attitude toward glycosuria has been subject to sharp criticism. Joslin² and his associates cast some doubt upon our observations, stating that glycosuria of 5 per cent or more and freedom from symptoms was not a reasonable compatibility. Even though we were certain of our records, emphatic criticism from such an authoritative and respected source led us to a review of our data and further experimental work. It is the purpose of this communication to present the results of this study.

From a diabetic population of nearly 2000 we selected one of the most severe and practically uncontrollable diabetics, if a normal blood sugar and freedom from sugar in the urine are considered the ideal. This choice was deliberate, as it was our purpose to demonstrate convincingly that even a severe case can be managed by our standards. We freely admit that it is hazardous to generalize about diabetic therapy, yet we are convinced that if a diabetic of his degree of severity can carry on satisfactorily without complications in spite of his glycosuria, the treatment of the milder and moderately severe patients will hardly offer any difficulties or hazards if our criteria are employed. The patient whose history will be presented in detail had a blood cholesterol of 250 mg per cent, the free fatty acid level 1.2 per cent, the urea nitrogen 15 mg per 100 ml, and the creatinine 1.2 mg per 100 ml. His aim has been to maintain his urine free from sugar and albumin (urinary albumin estimation for liver disease was negative). The patient, who was 50 years of age, had been treated for 10 years, approaching the normal level using three to four daily insulin injections (1) and (2) guided by our criteria in which only one dose of 40 units of protamine insulin was used and the glycosuria was disregarded. Throughout the 46 days of the study, the patient was under 100 mg per 100 ml of blood sugar, with a total of 2200 units of protamine insulin.

* Received for publication April 25, 1941

From the Department of Medicine, Cornell University Medical College, served the patient
Sage Institute of Pathology in affiliation with the New York Hospital, New York, cooperation

patient department for three years, during which period he revealed a 4 plus glycosuria most of the time he visited the Clinic. The two hospital periods are not ideally comparable, because on his first admission he was on the general wards. Although the observations and laboratory data are not as detailed and as carefully supervised as they were over the second period of study on the Metabolism Ward of the Russell Sage Institute of Pathology, nevertheless the available data are accurate and reliable.

CASE REPORT

The patient is a 40-year-old male. His family history did not reveal any diabetes. He had never been robust. In childhood he had scarlet fever, following which he was said to have had acute glomerular nephritis. As an adult he had sinusitis and alveolar abscesses. From three years prior to the onset of his diabetes, he had drunk heavily of liquor at irregular intervals. His usual weight has been 58.5 kg (130 lbs).

In 1928 he developed the classical symptoms of diabetes, for which he was hospitalized. He responded to the therapy employed and on discharge was receiving 45 units of soluble insulin and a moderate carbohydrate diet. During the hospital period he acquired considerable knowledge about diet, insulin and diabetic management. For three years he was somewhat faithful to instructions but then lapsed into gross carelessness. He had little medical supervision for the following six years from 1931 to 1937. During this period he ate as he pleased, consumed quantities of beer, took insulin irregularly and in varying quantities, at times up to 100 units a day. As a result of this haphazard regime he had three episodes of ketosis, requiring hospital care, and while not under supervision in the hospital he experienced frequent and numerous insulin reactions characterized by convulsions and coma. Many of these occurred at night and were quite alarming. Because of the frequency and severity of these reactions he was admitted to the New York Hospital for study.

Period 1 General Medical Ward On admission April 17, 1937, the patient was in mild ketosis, which was difficult to eliminate. Since he had a 3 plus glycosuria with this ketosis, 25 units of regular insulin were administered and this was followed by a profound insulin reaction. After proper therapy for this condition, attempts to treat his diabetes with the idea of reducing the blood sugar to normal levels resulted in severe insulin reactions. After three days of careful vigilance and intensive insulin therapy his urine became sugar free, and he was placed on a diet of P 70, F 60, C 300. From that time the medical staff made every effort to control his diabetes by the usually accepted laboratory criteria that is normal blood sugar and absence of glycosuria. To do this, numerous combinations of insulin, regular and protamine, were tried but without success. The glycosuria was present at irregular intervals and quite heavy. He also showed acetone bodies on 21 of the 42 hospital days. His blood sugar (fasting) ranged from 40 to 428 mg. Even though a constant regime was attempted without any changes the patient would have insulin reactions on certain days. There were no evident complications which could explain this difficulty in regulation. The management of his pyorrhea alveolaris and dental caries had no effect. There were no other evidences of infection, and a roentgenogram of his chest revealed no pulmonary disease. The peripheral vessels were described as "slightly sclerotic," and soft tissue roentgen-rays of the legs showed a moderate arteriosclerosis with beginning calcific changes, particularly about the ankles. At the end of a 42-day period on the General Ward the patient was receiving 85 units of insulin per day (35-10-30-10 mid night), and the diet mentioned above. The results were never considered satisfactory as at no time could one maintain his urine sugar free and his blood sugar at normal levels without severe reactions. Furthermore an attempt to reduce the insulin resulted in glycosuria and ketonuria. The patient left the hospital

for financial reasons. His greatest weight during this period was 66 kg (145 lbs), his lowest (that at the time of discharge) was 63 kg (140 lbs).

Period 2 Out-Patient Department The patient was then followed in the Out-Patient Department for nearly $3\frac{1}{2}$ years, where he was seen a total of 44 times or slightly more often than once a month. Efforts to reduce the hyperglycemia and the glycosuria were continued and more than 30 different combinations of regular and protamine insulin were tried. Such changes often were accompanied by the occurrence of mild ketosis on the one hand, and much more frequently, to the despair of the patient, severe insulin reactions on the other. When he reported to the Clinic the 24-hour specimen usually revealed a 4 plus glycosuria. The patient was almost entirely free from the usual symptoms of diabetes, but during $2\frac{1}{2}$ years of this, his weight had fallen about 8 kilos. His diet was never weighed and an estimation of his diet at each visit was usually below the prescription. We appreciate that this estimate is not precise but nevertheless it gave us an idea that he was not eating as much as he should have. It was estimated that his diet averaged about P 65, F 70, C 180 to 200. In spite of mild insulin reactions the patient led essentially a normal life. He appeared to all observers capable of gainful occupation, although a small income made this unnecessary. He lived alone in a small apartment, ate his meals in restaurants and was in general frank and cooperative with us. He occasionally indulged in alcoholic bouts resulting in irregular eating periods and insulin reactions. He had occasional colds but no other serious infection, and no evidence of circulatory insufficiency in the extremities. Since numerous doses of insulin were not productive of the ideal results demanded by some workers in the field of diabetes and since the multiple injections caused him considerable inconvenience as well as undesirable reactions we treated him by means of one dose of insulin daily, using the criteria we mentioned above. He was encouraged to eat his total diet, P 70, F 70, C 300. This was covered by 50 units of protamine insulin given in the morning, and he was also advised to have a glass of milk and three crackers at bedtime. At the end of 10 months on this regime of one daily dose of protamine insulin, although he never ate as much as was advised although he still took alcohol occasionally, and although he always revealed a 4 plus glycosuria in the 24-hour specimen, he had maintained his weight, had no ketosis, had complete freedom from symptoms of diabetes, and only most infrequently mild insulin reactions. There was no doubt in the patient's mind nor in ours that the latter regime suited him best. We were interested at this point to obtain some quantitative data in connection with this treatment, and therefore suggested that he enter the Metabolism Ward of the Russell Sage Institute of Pathology for further study.

Period 3 Metabolism Ward of the Russell Sage Institute of Pathology On admission October 19, 1940, the physical examination revealed little contributory. He had no complaints, and the detailed laboratory data are in the tables below. During his period of stay the following laboratory determinations were made. The urea clearance tests were 83 per cent and 105 per cent of the normal. Blood cholesterol taken at weekly periods varied from 212 mg per cent to 282 mg per cent, the free cholesterol being 41 per cent of the total. The basal metabolic rate varied from —1 per cent to —9 per cent. The hippuric acid test and prothrombin estimation for liver function were within normal limits. Roentgen-ray (soft tissue technic) showed no increase in calcification of leg arteries as compared with films of three years ago and roentgen-ray of the chest revealed no abnormalities. Throughout the 46 days of the test period the patient was maintained on a diet of P 70, F 80, C 300, a total of 2200 calories. This he consumed quantitatively taking 50 to 60 units of protamine insulin daily. The diet was weighed, prepared, calculated and checked by a trained nursing and dietetic staff. Neither the staff nor the patient's roommate ever observed the patient obtaining extra food. His attitude throughout was one of complete cooperation.

He took mild and fairly regular exercise by walking and pushing wheelchairs in the corridors. As there was a slight ketonuria on admission in some of the fractional specimens the protamine insulin dosage was increased from 50 to 60 units, and although it abolished the ketone bodies from the urine it produced insulin reactions before breakfast. He was finally given 55 units of protamine insulin, and even then there was occasional mild ketonuria in one of the fractional specimens, but no reactions. During his entire hospital stay he was questioned daily by two of us as to the occurrence of symptoms of diabetes. He never complained of thirst, hunger, or weakness. Frequency of urination varied from four to seven times a day, and only on six occasions in seven weeks did the patient void during the night. His total fluid intake varied from 900 to 2800 cc a day. His strength, which had never been excellent, remained about the same during the period of study. A careful record was kept of the patient's weight throughout his stay. Every specimen of urine voided was tested for sugar and acetone qualitatively, and then the specimens were pooled and examined quantitatively for total glucose, nitrogen and chlorides excreted in 24 hours. Creatinine determinations were made daily to serve as additional checks on the total output. The stools were not analyzed for nitrogen, but 10 per cent nitrogen loss by this route was assumed. Blood sugar determinations were done at weekly intervals at definite time periods indicated in the second table. Standard methods were used for all laboratory procedures.

COMMENT

Our clinical and chemical observations reveal certain positive facts. These facts completely and sharply support our previous publications,¹ wherein we categorically stated that even though our patients were excreting large quantities of glucose during a 24-hour period, they "were free from symptoms of diabetes and were in nitrogen equilibrium." We emphasized the fact that during the experimental period the weight loss was not appreciable. This conclusion has been substantiated in the experiment herein presented. The figures in table 1 show that in 46 days the patient lost 0.6 kg with a glycosuria of 200 gm + for 5 days, 100 gm + for 14 days, 50 gm + for 21 days, and below 50 gm for 6 days. When this loss of sugar in the urine is translated into the calories lost it is seen in the last 2 columns of the table that the available calories per day varied from 21.3 to 34.5 per kilogram, which is below the Aub-DuBois standards for a man of his age. Of course, these findings are out of line with accepted concepts, yet our chemical analyses have been consistent throughout and the present figures support our former results.

The thought that a patient treated with protamine insulin may reveal a glycosuria and be considered as adequately controlled has been commented on by others,³ and even such experienced and conservative observers as the Joslin group¹ have disregarded a 24-hour glycosuria up to 10 per cent of the total carbohydrate intake. The controversial point, therefore, is not the glycosuria but its magnitude. What shall we use as a standard? Shall loss of glucose be 10 per cent, 20 per cent or more of the total carbohydrate intake? It seems to us one cannot make this decision in an arbitrary fashion. To be of value such a standard must be based on either clinical evidence, experimental evidence or both. At present no such evidence is avail-

TABLE I
Experiment started 10/20/40, ended 12/4/40

Patient H P			Diet P 70 F 80 C 300			Total calories			2200		Total N intake 11.0 gm		
Day of Experiment	Weight in kg	Urine							N balance	PZU units	Calories lost in 24 hrs	Available cal per kg	
		Volume	S G	Glucose gm	Glucose %	Glucose and acetone in fraction of specimens *	Chlorides	Total N					
1	59.55	2380	1.027	158	6.6	4 1 4 4 tr 0 tr tr	12.1	7.77	2.23	50	632	21.2	
2		2010	1.024	167	8.3	4 4 4 4 1 1 1 0 0 0 0 0	7.2	5.77	1.23	50	668		
3	60.23	2860	1.029	216	7.6	tr 4 4 4 4 4 4 1 1 1 tr tr 1	13.2	9.00	1.00	50	864	21.3	
4		3810	1.026	225	5.9	4 4 4 4 4 4 2 0 0 0 2	17.2	10.50	-0.50	50	900		
5	59.43	3610	1.029	212	5.9	4 4 4 4 4 4 0 ft 0 0	19.5	10.82	-0.82	60	818	23	
6		2705	1.034	200	7.4	4 4 4 4 4 4 1 2 2 tr tr	12.5	11.10	-1.10	60	800		
7	59.45	1065	1.029	53	5.0	4 4 4 4 4 4 0 0 0 0	5.8	3.57	6.43	60	222	33.2	
8		1935	1.024	50	2.6	0 0 1 3 4 4 2 2 0 0 0	12.0		-0.35	60	200		
9	60.15	2285	1.026	84	3.7	2 4 4 4 4 4 0 0 0 0 0	15.1	8.92	1.08	60	336	31	
10		2290	1.023	76	3.3	2 2 4 4 4 4 0 0 0 0 0	14.9	8.30	1.70	60	304		

* Upper figure = Glucose, the figure represents the degree, ex 4 = 4 + Lower figure = Acetone

TABLE I—Continued

Day of Experiment	Weight in kg	Urine							N balance	PZI units	Calories lost in 24 hrs	Available cal per kg
		Volume	S G	Glucose gm	Glucose %	Glucose and acetone in fractional specimens *		Chlorides	Total N			
11	59 51	1725	1 018	38	2 2	tr 0	4 4 0 0	tr 0	7 10	60	132	33 8
12		1365	1 021	18	1 2	tr 0	0 4 0 0	4 ft 0 0	7 82	60	72	
13	59 99	1190	1 030	57	3 9	4 4 0 0	4 4 0 0	tr 0	8 40	50	228	33
14		2330	1 028	88	3 8	3 4 0 0	4 4 0 0	4 0 0 0	9 35	50	352	
15		1950	1 034	103	5 3	4 4 0 0	4 4 0 0	4 4 0 0	9 40	50	412	
16	59 69	1990	1 033	100	5 0	4 4 tr	4 4 0 tr	4 1 0 0	10 35	50	400	33
17		1970	1 035	95	4 8	4 4 tr	4 4 0 0	4 1 0 ti	10 20	50	380	
18	59 65	2185	1 034	200	9 2	3 4 vft	4 3 0 0	3 3 0 0	9 97	50	800	23 4
19		1105	1 017	40	3 6	4 4 0 0	4 vft 0 vft		7 67	50	160	
20	59 67	1860	1 020	56	3 0	4 4 0 0	4 2 0 tr		2 33	50	224	33
21		1840	1 032	106	5 8	4 4 0 0	4 4 ft ft	4 4 0 0	2 03	50	424	
22	59 06	1460	1 036	107	7 3	4 4 0 0	4 4 ft 0	4 tr 0 1	1 49	50	428	30

TABLE I—Continued

Day of Experiment	Weight in kg	Urine							N balance	PZI units	Calories lost in 24 hrs	Available cal per kg
		Volume	S G	Glucose gm	Glucose %	Glucose and acetone in fractional specimens *		Chlorides	Total N			
23		1110	1 038	62	5 6	4 4 4	4 4 4	6 5	8 03.	50	218	
24	59 41	2090	1 030	95	4 6	4 4 4	4 4 4	11 0	9 40	50	380	30 7
25		1045	1 034	60	5 7	4 4 4	4 4 4	6 3	7 55	50	210	
26	58 17	2300	1 036	131	5 7	4 4 4	4 4 4	10 9	9 50	50	524	28 8
27		1180	1 039	83	7 1	4 4 4	4 4 4	5 3	7 74	50	332	
28	59 12	1445	1 030	65	4 5	3 4 4	4 4 4	8 0	9 88	50	260	32 8
29		2050	1 026	87	4 3	4 2 4	4 4 4	8 7	8 85	50	318	
30	59 26	2515	1 033	171	6 8	4 4 4	4 4 4	8 9	9 95	50	684	26 6
31		960	1 032	53	5 6	4 4 4	4 4 4	3 0	8 57	55	222	
32		1095	1 020	5	0 5	1 0 0	0 0 0	3 8	9 30	55	20	
33	59 49	1935	1 027	91	4 7	4 4 4	4 4 4	5 0	7 55	55	364	30 8
34		1995	1 028	91	4 6	3 4 4	4 4 4	8 2	8 50	55	351	

TABLE I—Continued

Day of Experiment	Weight in kg	Urine								N balance	PZI units	Calories lost in 24 hrs	Available cal per kg
		Volume	S G	Glucose gm	Glucose %	Glucose and acetone in fractional specimens *			Chlorides	Total N			
35	59.05	2490	1.033	150	6.0	4 3 4 4 0 0	tr	0	11.4	10.08	55	600	27
36		2170	1.039	167	7.7	4 4 4 4 0 0	0	ft	6.3	10.63	55	668	
37	58.50	1365	1.021	37	2.7	4 4 4 0 0 0	0	0	5.9	9.16	55	128	34.4
38		1190	1.037	53	4.5	3 3 3 0 0 0	tr	ft	5.9	8.00	55	222	
39	58.94	1140	1.023	13	1.2	4 4 2 0 0 0	tr	0	6.5	8.62	55	52	34.5
40		2440	1.034	128	5.2	4 4 4 0 0 0	0	0	10.0	8.57	55	512	
41	59.22	2690	1.036	173	6.4	4 4 4 4 0 0	ft	0	10.1	11.52	55	692	25.5
42		1895	1.039	107	5.7	ft 4 4 4 0 0	tr	1 0	7.0	9.85	55	428	
43		1480	1.033	68	4.6	4 4 4 0 0 0	0	0	7.5	10.28	55	252	
44	58.95	2250	1.030	106	4.7	4 4 4 0 0 0	0	0	9.5	9.42	55	424	30.1
45		1575	1.033	75	4.8	4 4 4 0 0 0	0	0	6.9	7.95	55	300	
46	58.96	1520	1.032	70	4.7	4 4 4 0 0 0	0	ft	7.5	9.40	55	280	32.05

able. No one is in a position to state authoritatively whether a glycosuria of 5, 10 or 50 per cent of the total carbohydrate intake is the ideal. We can say, however, from experimental and clinical observation that patients treated with protamine insulin may excrete large quantities of glucose over the periods we have observed and yet reveal no deleterious effects. Furthermore, we are convinced that it is dangerous to attempt too fine a regulation because the excretion of sugar is so irregular and unpredictable that reactions may ensue. Even though the diet, environment, physical and probably mental state of our patient were as constant as experimental conditions permitted, yet the glycosuria was most irregular and extremely variable. With 55 units of protamine insulin daily it varied from 55 to 173 gm in 24 hours. Furthermore, a slight increase in the insulin dosage resulted in reactions. Chiefly because of a mild ketosis when he entered the metabolism ward we increased his insulin dosage from 50 to 60 units. Three days following this change the ketone bodies disappeared but the patient exhibited, in the presence of a glycosuria, insulin reactions quite severe and alarming on two occasions. This, in addition to subsequent symptoms of milder hypoglycemic episodes resulted in the reduction of the insulin to its original quantity of 50 units. When this dosage was resumed the acetone reappeared. It was only found in some of the fractional specimens in small traces, and it did not bear any relationship to the amount of glucose in the specimens in which it was present. Quite often faint traces of acetone were found in the fractional specimens that *were sugar free*, usually the before-breakfast specimen, and at the following voiding the specimen again showed a 4 plus glycosuria but no acetone. When such traces of acetone were found in only a single specimen, the quantity was too small to react chemically on pooling the 24-hour urinary output. In general, the urinary volume and the specific gravity paralleled the glycosuria, but there were many instances in which this relationship could not be demonstrated. During the first six days of admission the volume varied from 2010 cc to 3810 cc. This we attributed not only to the magnitude of the glycosuria, but also to the order that the patient drink fluids freely and often, and to the additional 6 gm of salt given daily. When the salt capsules were discontinued the urinary volume decreased. The curious fact was that *at no time* did the patient complain of thirst. He had to be "forced" to drink. The excretion of chlorides was not very illuminating except that it followed roughly the urinary output, rising also when salt was given in addition to the salt in the food. On such days the chloride excretion was high. Once each week the blood sugar was determined at definite intervals throughout the day. It is clear from table 2 that the blood sugar varied from week to week even though the experimental conditions with the exception of slight changes in the dosage of insulin were similar. Furthermore, the changes in quantity of insulin appear to have had no constant effect on the height of the blood sugar curve.

It was our purpose at the outset to confine ourselves to facts and avoid speculative considerations. Our reluctance to enter into hypothetical and

TABLE II
Blood Sugar and Cholesterol Content for Patient *

Date	8 a m	11 a m	4 p m	9 p m	Cholesterol	Remarks
10/21/40	53	394	300	230	250	50 units protamine insulin
10/28/40	35	172	272	306	212	60 " " "
11/ 4/40	159	312	500	263	243	50 " " "
11/11/40	91	150	166	136	282	50 " " "
11/18/40	68	248	300	365	250	50 " " "
11/25/40	65	208	197	174	250	55 " " "
12/ 2/40	78	300	300	267	253	55 " " "

* The values for the blood are expressed in milligrams per hundred cubic centimeters

controversial discussions is based on the experience that after speculations are repeated often enough they are accepted as facts. This is particularly true when one's opportunities to test a given hypothesis are limited. Examples of this are the rooted ideas that hyperglycemia causes arteriosclerosis and predisposes the diabetic to infections. Of course, the most ardent protagonists of these hypotheses admit that the evidence for such assumptions is not very conclusive, yet these statements continue to be perpetuated and quoted as established facts. Apropos of these theories, we have been asked what will happen to our patients over a long period of time, say 25 years, if we treat them by our method and disregard the glycosuria. Since our experience is only about four years old we cannot speak authoritatively for longer periods. We were unable to show progressive sclerosis of the leg vessels by roentgenograms, in this severe diabetic, although we recorded a continuous glycosuria for three years. Furthermore, this patient had no more colds than a non-diabetic and his lungs were clear at all times. Our experience has been similar with other patients. Consequently, although we do not know what may happen to such patients over a longer period of time, our experience with shorter periods prompts us to hazard the thought that they will not suffer from unusual complications. We make this statement reservedly, fully realizing that there is a huge hiatus between impressions and factual knowledge.

Criticism may be directed justly at our therapy for not rendering the urine ketone free at all times. We would have been quite discouraged at our inability to achieve this end, if we did not have the patient's record of three years ago. At that time he revealed traces of acetone just as irregularly even though every attempt was made to render the urine sugar free with 85 units of insulin in four divided doses, and when attempts were made to increase the insulin or reduce the food intake, hypoglycemic reactions supervened. We can offer no explanation for our failure other than the severity of his diabetes. Yet at present this patient is much happier than he was then, because he has only occasional mild reactions, he has reduced the number of injections to one a day, and he has been able to reduce the dosage of insulin as well. He reports to the out-patient department at regular intervals and continues to reveal a + plus glycosuria but no acetone, at every visit. These

are 24-hour specimens. We have asked him to examine occasional specimens for acetone which he has reported as negative. Clinically, he is maintaining his weight, has no symptoms of diabetes, and has no fear of reactions, criteria which we have proposed and consider satisfactory when protamine insulin is used in the treatment of diabetes. Our experience with this method of treatment has been most gratifying and we hope that others will try it. The details of the method have been published,¹ and they demonstrate that our system has simplified diabetic therapy both for the physician and, what is more important, for the patient.

SUMMARY AND CONCLUSIONS

A severe case of diabetes mellitus is presented in which the treatment with multiple injections of insulin, aiming at a normal blood sugar and sugar free urine, failed to produce as good clinical results as a single dose of protamine zinc insulin, with no attempt to abolish hyperglycemia and glycosuria. On the latter régime, weight was maintained, the patient remained in positive nitrogen balance, he was free from symptoms of diabetes, but occasionally suffered from mild insulin reactions. He was maintained on a diet of protein 70 gm, fat 70 gm, carbohydrate 300 gm, with 50 to 60 units of protamine zinc insulin. Under constant experimental conditions, the glycosuria showed enormous and unpredictable variations. Despite the heavy and continuous glycosuria for three years the patient has not developed any more colds or other infections, than the non-diabetic. His renal function shows no impairment, his atherosclerosis no demonstrable increase.

It is not unlikely that the view point toward glycosuria, when using protamine insulin, will have to be reconsidered, and whereas a good many physicians may still prefer a sugar free urine when treating diabetes mellitus, we want to emphasize that we do not disagree with this plan. If our patients are sugar free and still fulfill the criteria which we have outlined, we do not increase their carbohydrate intake so as to make them excrete sugar. However, when we find that it is extremely difficult to maintain the urine sugar free and avoid reactions, unequivocally we prefer the glycosuria, not only because it makes the patient more comfortable, but because our experience to date has convinced us of its harmlessness.

BIBLIOGRAPHY

- 1 TOLSTOI, E., and WEBER, F. C., JR. Protamine zinc insulin: a metabolic study, *Arch Int Med*, 1939, **LIV**, 91.
- TOLSTOI, E., and WEBER, F. C., JR. Protamine zinc insulin: a clinical study, *Arch Int Med*, 1940, **LVI**, 670.
- 2 Correspondence, *Jr Am Med Assoc*, 1940, **CV**, 1038.
- 3 Editorial: Protamine insulin and diet in diabetes mellitus, *ANN INT MED*, 1938, **XI**, 2048.
- 4 JOSLIN, E. P. Diabetes and protamine insulin, *Mil Surg*, 1938, **LXXXII**, 1.
- WHITE, P. Protamine insulin in the treatment of juvenile diabetes, *South Med Jr*, 1938, **XXXI**, 15.

SUBACUTE BACTERIAL ENDOCARDITIS; AN ANALYSIS OF FIFTY CASES WITH AUTOPSY FINDINGS *

By HAROLD COMONFORT DENMAN, M D , F A C P , *Brooklyn, New York*

COBURN,¹ in his study of rheumatic disease, observed that although this disease is found with great frequency among children and in young adolescents on the medical wards, non-hemolytic streptococcus endocarditis has been infrequent in this age group at the Presbyterian Hospital and has been observed only once on these wards in a patient under 10 years old. This is in agreement with the findings of others. Blumer,² in studying 317 cases of subacute bacterial endocarditis, found only one under the age of 10 years. At the Great Ormond Street Hospital for Children, Schlessinger³ found but 10 cases of subacute bacterial endocarditis in reviewing the postmortem records which had been collected over a period of 65 years. These contain 341 cases of rheumatic endocarditis. Rost,⁴ in collecting the cases of subacute bacterial endocarditis occurring in children, says that "in Libman's first 149 cases of subacute bacterial endocarditis, only one occurred in a child under 10 years of age. Observations on children under 14 years of age are scarce in the literature. One rarely finds this condition mentioned and a review of the postmortems of the past half century lists only 64 cases in children." However, although the common type of bacterial endocarditis associated with rheumatic heart disease is a non-hemolytic streptococcus infection, other types of bacterial endocarditis occur in patients with hearts damaged by the rheumatic process. These have included, among many organisms, the hemolytic staphylococcus, the hemolytic streptococcus, the pneumococcus, *Staphylococcus aureus*,⁵ *Staphylococcus albus*,^{6, 7} gonococcus,⁸ and the influenza bacillus. Bacterial endocarditis caused by the pyocyaneus bacillus has been reported by Lenhartz⁸ and Thayer,⁹ and by the *Bacillus anthracis*, by Young and Blumer.¹⁰

Coombs,¹⁰ in 1924, determined the average age at onset of the rheumatic infection in 253 rheumatic children who had come under his care to be 10.2 years.

Congenital imperfections of the valves sometimes form the ground work of these bacterial infections. In 1844 Sir James Paget¹¹ called attention to the frequency with which bicuspid pulmonary and aortic valves are the seat of subsequent disease. This has been emphasized more recently by Lewis and Grant,¹² who brought forward evidence that congenital lesions of the aortic valves often determine subsequent subacute infective endocarditis. Maude E. Abbott¹³ has noted and emphasized the frequency with which

* Received for publication September 24, 1940.

From the Medical services of St. Peter's and Kings County Hospitals, Brooklyn, New York.

bacterial endocarditis is superimposed on congenitally defective hearts, 17.6 per cent in 555 cases of significant congenital heart disease.

With these observations in mind the writer has analyzed 50 consecutive postmortem examinations on patients with subacute bacterial endocarditis who have come under his observation.

In subacute bacterial endocarditis we have disease in which the most prominent features are distinctly not cardiac. "An ill-defined malaise, slight anemia, some loss of weight, irregular fever, sweats, erratic pains in the limbs, muscles, back or joints, or fingers, or toes, areas of redness or tenderness developing on the hands or feet—one or more of these in any patient in whom a critical examination of the heart fails to pass it as organically sound, should raise our suspicions and should point to a special examination for definite stigmata of endocardial infection." However, late in the disease the symptoms are mainly embolic in nature and an examination of these symptoms, as complained of on admission in the cases investigated, bespeak their variety. In this series, in the order of their frequency they were dyspnea, pain, fever, weakness, chills, vomiting, paralysis, anemia, cough, loss of appetite, loss of weight, nausea, palpitation, tarry stools, sore throat, hematuria, hemoptysis, coma, bad teeth, nocturia, convulsions, epistaxis, night sweats, incontinence, jaundice, constipation or diarrhea, and nervousness. These symptoms complained of on admission depended largely on the age of the patient. Those 10 years old or younger complained of the following: loss of appetite, weakness, fever, vomiting, convulsions, chills, loss of weight, throat infection, nervousness, bloody expectoration and cough. There was some variation from these symptoms in the group from 10 to 20 years of age, whose chief complaints were chills, fever, joint or muscular pains, tarry stools, weakness, vomiting, anemia, palpitation, heart pain, nodes and petechial eruption.

The age incidence in these 50 cases was

Up to 10 years	6
11 to 20 years	3
21 to 30 years	9
31 to 40 years	17
41 to 50 years	10
51 to 60 years	5

Six more cases were seen, but were excluded from this series because of their age and the possibility that their infectious endocarditis was a terminal manifestation rather than the primary cause of death. Their ages were 59, 66, 67 (two), 75, and 78 years.

There were 28 males and 22 females, 45 white and five colored patients.

The age incidence is of interest, for, as previously mentioned, many investigators have found non-hemolytic streptococcus endocarditis infrequently among children and young adolescents, and there is some question how early in life this condition can occur. The following case, not among the 50 in

this series, is mentioned because of the age of the patient, the implications of the case and the pathological possibilities it may engender

Case 1 The history is as follows. A female baby had been delivered of an American mother, Mrs McC, white, 40 years of age primigravida. It was a natural delivery. On the second day the baby was unusually quiet, she became lethargic with a slight bluish discoloration to the skin which deepened until death. The Wassermann reaction was negative for the baby and both parents. The autopsy findings showed a well-nourished white female infant. The head was negative, the lungs showed diffuse areas of atelectasis, the heart showed a small nodule two millimeters in diameter on the mitral valve which had the appearance of a vegetation (Figure 1). Otherwise the heart was negative, as were the other organs.



FIG 1 Baby McC, aged two days, a vegetation two millimeters in diameter on the mitral valve

Microscopic examination showed atelectasis of the lungs, normal myocardium. Section of the vegetation showed focal areas of endothelium in which there was an increase of connective tissue, and an absence of lining endothelial cells. It was regarded as a small focal scar on the mitral valve.

Fetal and infant endocarditis has been reported recently,^{14, 15, 16, 17} as well as an endocardial vegetation in an infant one year of age.¹⁸ Abraham¹⁹ reported a case of an infant four days old, presenting somewhat the same symptoms as the above, in whom thickened bicuspid aortic and pulmonary valves and a mural vegetation of the left ventricle were found at postmortem examination. Lawson and Palmer²⁰ reported three cases occurring in children aged six, eight and 10 years respectively and one case of *Streptococcus viridans* septicemia, without demonstrable valve lesions, in a child aged 12 months. Leech²¹ reported *Streptococcus viridans* endocarditis, proved

by autopsy in 15 cases in children, three of whom were under five years of age and one 21 months

Blood cultures before death were positive in 23 cases, sterile in 10, and were not taken in 17. That this diagnostic procedure was neglected in 34 per cent of patients dying of infectious endocarditis bespeaks the deceiving and misleading symptomatology of the disease, the complaints on admission being such as to divert attention from the primary disease to the complications, as illustrated by the following case

Case 2 M. B., a white female, aged 30 years, was admitted to the surgical service on September 23, complaining of pain in the left lumbar and the right iliac regions of the abdomen

The following history was obtained from the patient. Menstrual periods had been regular up to one year before admission, since which time periods of menorrhagia and metrorrhagia had been experienced. Two months before she had been admitted to another hospital for a sharp pain in the left groin radiating to the back. She was discharged 27 days later improved, the diagnosis being sacroiliac and intervertebral arthritis, a laceration of the perineum, and a lacerated cervix with fixation of the fundus to the left.

The past history was irrelevant. The onset of her menstruation was at 16 years of age; it had always been regular, every 28 days and of four to five days' duration, the last period occurring 17 days before admission. She had had 10 pregnancies six of which terminated spontaneously.

Physical examination revealed a white female, subacutely ill and poorly nourished. The teeth were in poor condition. The fauces, pharynx and tonsillar areas were moderately inflamed. The submaxillary glands were enlarged but not tender. The chest was normal. The cardiac apex impulse was one centimeter outside the mid-clavicular line. There were no murmurs. The abdomen was enlarged, there was spasticity of the muscles and tenderness in both lower quadrants. There was an herpetiform eruption about the lips. The temperature was 101° F., pulse 110, and respirations 22. The blood pressure was 136 mm Hg systolic and 86 mm diastolic.

The patient on admission presented the history and physical signs of a chronic pelvic infection.

Roentgen-ray examination showed a sacroiliac arthritis of moderate degree on the left side. There was no evidence of abnormality of the dorsal vertebrae. There was evidence of a productive arthritic process about the left halves of the second and third lumbar vertebrae. Stereoscopic examination of the hips revealed no evidence of abnormality. The femur was normal. Pyelograms also were negative. Catheterized urine showed no albumin or red blood cells, there was only an occasional white blood cell from each ureter.

The Wassermann and Kahn reactions were negative. The blood examination on admission showed red blood cells 4,000,000, white blood cells 9,300, polymorphonuclear leukocytes 83 per cent, lymphocytes 16 per cent, large mononuclear leukocytes 1 per cent. The hemoglobin was 70 per cent. Subsequent examination showed a steady drop of red blood cells to 2,750,000, and hemoglobin to 50 per cent, and a rise in white blood cells to 22,000, polymorphonuclear leukocytes to 92 per cent, with lymphocytes 8 per cent.

The patient was more comfortable in a dorsal recumbent position with the knee flexed. The abdominal tenderness became more prominent in the right lower quadrant increasing toward the right lumbar region. Pelvic examination showed no evidence of inflammation. There was a thick dark discharge from the lacerated, eroded and everted cervix, but no masses were felt and no tenderness was elicited. A rectal examination was negative.

Nineteen days after admission a pneumonitis occurred at the left base, with a rise in temperature ranging from 102° F to 105° F. The pulse was 120 to 140 and the respirations 16 to 32. Blood pressure was 100 mm Hg systolic and 70 mm diastolic. A few days later a similar area of pneumonitis was noted at the right base. Frequent examinations revealed no evidence of cardiac disease not concomitant with the prolonged fever. On the day before death, the thirtieth after admission, two petechiae were observed on the left conjunctiva.

The postmortem examination revealed the body of a young white gull about 30 years of age. There were many hemorrhages in the sclera of the left eye. A midline incision and removal of the sternum revealed the right lung adherent at the base, many small infarcts were present. The left lung showed infarcts with a large thrombus.



FIG 2 Numerous verrucae on the mitral valve

in the lower branch of the pulmonary artery. The heart was small and there were numerous verrucae on the mitral flap, they were red, granular and of bacterial origin. The spleen was twice the normal size with large emboli and showed numerous small infarcts. The left iliac vein contained a thrombus adherent to the wall of the vein and giving complete obstruction.

Microscopical findings were as follows. The lungs showed hemorrhagic infarcts, the heart, thrombotic changes continuous with the endothelial layer. There was a small area containing many polynuclear cells and bacterial colonies (Figures 3 and 4). The myocardium showed much fatty degeneration and new connective tissue

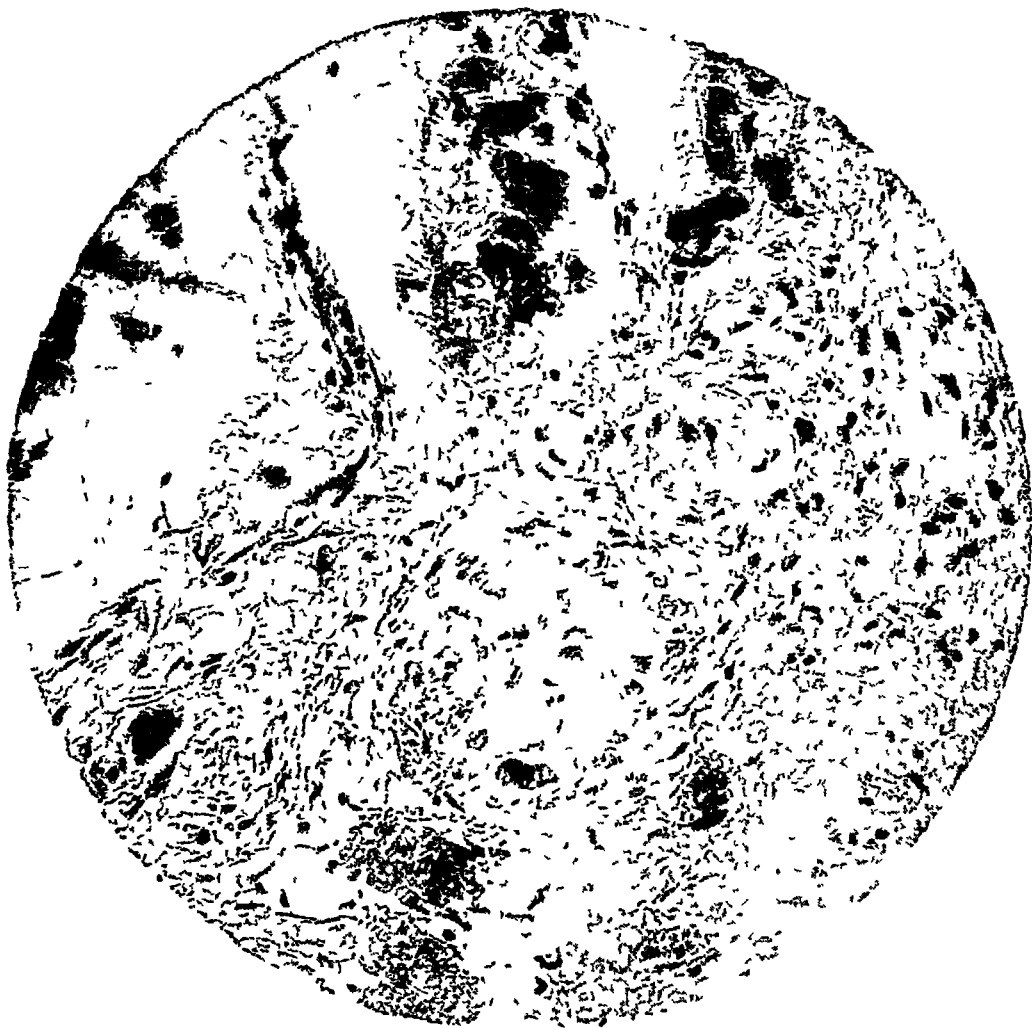


FIG 3 Aschoff body

formation. There were also hemorrhages in the myocardium between the fibers. The spleen showed infarction with areas of necrosis and perivascular round cell infiltration. The liver showed focal necrosis. Embolic glomerular nephritis and congestion were present in both kidneys. The adrenal glands showed marked degenerative changes, cloudy swelling and necrosis.

The cause of death was subacute bacterial endocarditis, viridans type, and multiple emboli with infarcts of the kidneys, spleen, lungs and the iliac veins.

This confusing surgical problem proved on postmortem examination to be purely medical. The history emphasized the gynecological aspect, tending to divert attention to the complications and from the cause as is so common in this condition. In retrospect, however, areas of embolic pneumonitis and tender kidneys were the clues overlooked. An early positive blood culture

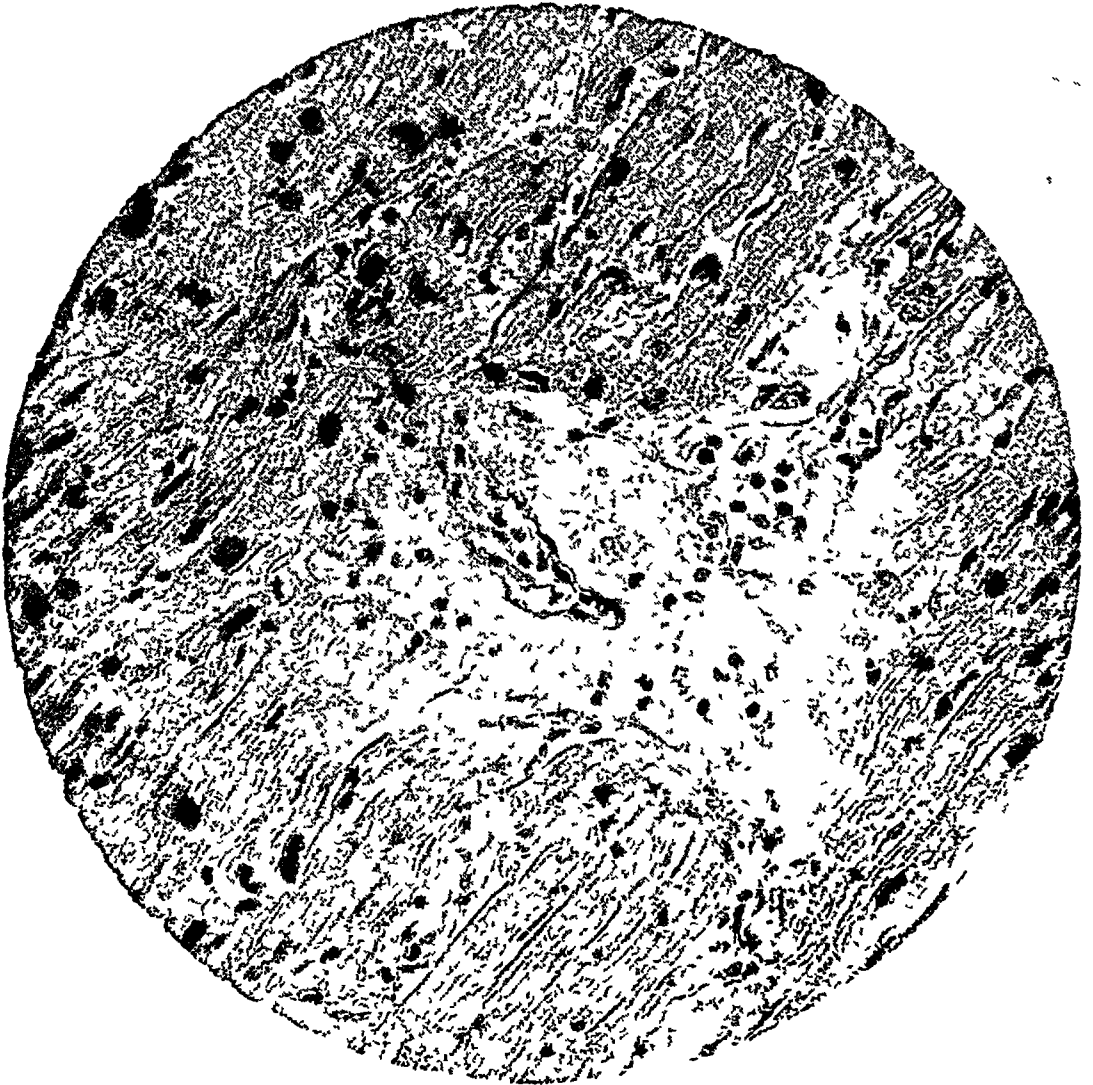


FIG 4 From the same patient as figure 3 Bracht-Wachter lesion

will explain what otherwise may develop into a confusing malady. The absence of red blood cells in the urine in this case is unexplained.

Of those patients showing a positive blood culture, the *Streptococcus viridans* was present in 19, and staphylococci were present in four, one of which had a mixed staphylococcus and *Streptococcus viridans*, and one of which showed a culture of a Gram positive bacillus.

The duration of subacute bacterial endocarditis is difficult if not impossible to estimate in the vast majority of cases. What may be taken as the

onset may be an incident in the course of the disease, or the patient may be wholly unaware of the fact that he is the victim of a serious illness until the occurrence of embolic phenomena

The former type is well illustrated in the following case of a verrucous endocarditis in a child four and one-half years of age

Case 3 E U was admitted to the hospital in convulsions, with fecal and urinary incontinence, tonic and clonic spasms and vomiting. The child died a few hours after admission

The history obtained from the parents was irrelevant. They insisted that the child had been in good health up to the morning of admission, when she experienced severe chills followed by a high temperature and convulsions

The postmortem examination revealed the body of a well-nourished and well-developed white female child four and one-half years of age. There were numerous small petechial spots distributed over the arms, legs and neck

The heart was free in the pericardial sac, and normal in size. The epicardium was congested and on section the myocardium was firm, somewhat edematous and nut-colored. The mural endocardium was clear; there was evidence of mural thrombosis. The mitral valve leaflets showed three areas of vegetation formation on the upper or auricular surface which coalesced to some extent. These vegetations were reddish-brown in color and stood out prominently against the normal appearing valve leaflet

There was a persistent thymus present weighing 50 grams. This gland was reddish-brown in color, moderately firm, and surrounded by its capsule

The head showed no abnormalities

Histological examination The thymus gland showed hyperplasia. The myocardium showed segmentation and fragmentation, a round cell infiltration was present. The heart valves showed a chronic fibrous endocarditis. There was a more recent exudate on the mitral valve, an increase in fibrous tissue, round cell infiltration, and absence of lining endothelial cells

The lymph glands showed reticulo-endothelial proliferation

The above case of a child who died 18 hours after the onset of an unexplained illness and who, hitherto, had been thought to be in good health by an unobserving mother, shows one of the problems in the diagnosis of this condition

The next case will illustrate the latter instance of failure to discover the true nature of this disease

Case 4 A P, a white Italian laborer, aged 39 years, was admitted to the medical service of Kings County Hospital, complaining of pain in his left leg of two days' duration. On the day before admission he worked as usual as a laborer, lifting and carrying bricks, and was not uncomfortable until night, when he experienced a pain in his left lumbar region radiating to his left hip. The pain became progressively worse, preventing sleep and making it impossible for him to stand erect

The family history was not contributory

The patient's previous personal history disclosed that he had had a similar attack one year previously, and since then six such seizures, less severe and shorter in duration than the present one

The physical examination showed a well developed and well nourished male complaining of acute pain in his left hip. The temperature was 100° F, pulse 90, and respirations 21. The blood pressure was 130 mm Hg systolic and 90 mm diastolic. His few remaining teeth were carious. His lungs and heart disclosed nothing ab-

normal The abdomen showed a moderate spasm of the recti muscles but no tenderness deep pressure in the left iliac region gave referred pain in the left hip The reflexes were normal The left leg was painful on motion A provisional diagnosis of osteomyelitis of the left hip was made and an orthopedic consultant concurred

The blood examination showed white blood cells 7,600, red blood cells 4,350,000, hemoglobin 75 per cent, polymorphonuclear leukocytes 89 per cent, mononuclears 4 per cent, lymphocytes 7 per cent The blood Wassermann and Kahn reactions were negative, blood culture showed a *Staphylococcus aureus*

Operation was performed the same day for an osteomyelitis of the left hip, and examination of the scrapings confirmed this opinion

The subsequent course was unfavorable, the patient presented the signs and symptoms of cerebral irritation and died on the ninth day of hospitalization

Postmortem examination of the tissues showed an embolic encephalitis, cloudy swelling of the myocardium, emboli, fragmentation, segmentation and a subacute endocarditis of the aortic cusps, and an ulcerative aortitis The lungs showed chronic passive congestion and anthracosis, the spleen, numerous bacterial emboli and infarcts There was an infarction of the ilium On removal of the right kidney there was noted a diffuse hemorrhagic infiltration into the retroperitoneal tissue which extended down the right side into the pelvis proper and encircled the rectum

In this study of the postmortem cases under consideration there was no case of congenitally deformed heart, and not all showed evidence of previous valve damage, although evidence of old subendocardial infiltration was noted This is readily understood as myocardial infiltration is a characteristic feature of rheumatic carditis Of 23 cases coming to postmortem examination, 22 showed characteristic perivascular, Aschoff bodies ⁵

"Subacute bacterial endocarditis never develops in a previously normal heart, but rather in those who have some abnormality of the valves or endocardium, either rheumatic or congenital in origin In general it may be said that 20 to 25 per cent of all cases suffering from valvular disease succumb to bacterial endocarditis" ²² However, fatal subacute bacterial endocarditis may develop soon after the initial rheumatic invasion, so soon after as to be a continuation of this process In one child three months elapsed between the primary attack of rheumatism and death from subacute bacterial endocarditis

The location of the verrucae when found on one valve only was as follows

Mitral	21
Aortic	10
Pulmonic	1
Tricuspid	1
Mural	2
Epicardial	1 ²³

When more than one valve was involved, they were found in the following combinations

Mitral, aortic and tricuspid	1
Mitral and tricuspid	2
Mitral and aortic	3
Mitral and mural	4
Aortic and tricuspid	2
Mitral aortic and mural	1
Aortic and mural	1

Levine expressed the opinion that the vegetations of subacute bacterial endocarditis are usually found on postmortem examination to involve more than one valve, but when they are confined to one valve they are almost as common on the mitral as on the aortic leaflets²²

Three hearts showed old healed verrucae with active vegetations also present. Two showed healed vegetations on postmortem examination, one of these, previously reported,²² showed a healed ectodermal lesion and an active secondary focus in the adventitia of the left renal artery, the other showed healed verrucae on the aortic valves. A brief summary of this latter case may be of interest for it aptly illustrates the observation of Libman²⁴ regarding patients in the bacteria free stage of the disease. Such patients have overcome the active infection, but have sequelae, such as subacute and chronic glomerular nephritis, progressive anemia, embolism and splenomegaly. They have recovered from the infection of the heart valves but die as a result of the damage that has been inflicted during the active, infective stage of the disease. They invariably succumb to the pathological changes necessary to overcome the active process.

Case 5 F. S., a white boy, nine years of age was admitted to the medical service of St. Peter's Hospital, complaining of vomiting, weakness and pain over the heart.

The following history was obtained from the patient. The present illness started two weeks before admission, with a "cold," herpes on the lips, and a gradually progressing weakness with loss of appetite and weight. The patient became breathless on exertion and a low grade irregular fever was noticed.

The family history was irrelevant. The patient had had the usual childhood diseases and frequent sore throats.

His temperature on admission was 99.6° F., pulse 110, respirations 24. The blood pressure was 118 mm. Hg systolic and 76 mm. diastolic.

Physical examination revealed a white boy acutely ill, pale and moderately emaciated. The tonsils were inflamed and cryptic. The heart was enlarged to the left. The apex impulse was in the fifth interspace outside the midclavicular line. There was a rough systolic murmur of maximum intensity at the apex, partially replacing the first sound and transmitted to the axilla. A short presystolic murmur was present. There was no thrill palpable. The abdomen was normal.

The diagnosis on admission was rheumatic endocarditis.

Blood examination showed red blood cells 3,425,000, white blood cells 15,700, polymorphonuclear leukocytes 82 per cent, small lymphocytes 10 per cent, large lymphocytes 8 per cent, hemoglobin 70 per cent. The red blood cells showed normal morphology. The urine was turbid, amber in color, with a specific gravity of 1.039. There was no albumin, sugar, pus cells or red cells present. The blood sugar, creatinine and urea nitrogen were within normal limits. Sedimentation time was 20 minutes in the first tube and 15 minutes in the second on admission, it went to 13 minutes and later rose to 29 minutes. Fragility began at 40 per cent sodium chloride and ended at 32 per cent. The blood Wassermann reaction was negative. The first positive staphylococcus blood culture was obtained three weeks after admission. The throat culture showed a preponderance of staphylococci and streptococci, Gram negative diplococci were also present.

On admission and while under observation the only suggestive signs of an infectious endocarditis were an increasing anemia, and petechiae which appeared in both conjunctivae in the early stages of this disease. During the period of hospitaliza-

tion, three and one-half months, the patient had two attacks of an embolic pneumonitis. He received two small transfusions of 250 cubic centimeters each and was discharged with a normal temperature, pulse and respiration.

The diagnosis on discharge was subacute bacterial endocarditis, staphylococcus bacteremia, but owing to the apparent improvement of this patient, the sterile blood culture on discharge, and the absence of embolic phenomena, except the early petechiae, the correctness of this diagnosis was doubted.

This patient was again admitted to St. Peter's Hospital three months later with signs of cardiac decompensation.

The history on this second admission was that he had been enjoying fair health while at home until one month previously, when gradually increasing dyspnea was noticed. He had been allowed up out of bed and even permitted to go down to the street to play, four stories below.

The physical examination at this time showed a cyanotic, orthopneic boy suffering from cardiac decompensation. There were basal râles in both lung fields. The heart was enlarged. The apex impulse was in the fifth intercostal space almost in the anterior axillary line. There was a soft systolic thrill at the apex with a harsh systolic pericardial rub, and a rough to-and-fro pericardial rub at the base. Capillary pulsation and a Corrigan type pulse were present. The liver was not enlarged. The spleen was enlarged. The fingers were clubbed to a marked degree.

During the second admission to the hospital, the physical signs were those of severe cardiac embarrassment owing mainly to an adhesive pericarditis. Pleural and pericardial effusion were present and fluid was withdrawn whenever necessary for the relief of the patient. Examination of this fluid showed it to be bloody and sterile on culture.

Repeated blood cultures were sterile.

The patient died eight months after his second admission with signs of cardiac failure.

Postmortem examination revealed marked biliary pigmentation of the scleral conjunctiva, extreme emaciation of the upper part of the body, edematous lower extremities, and fluid in the abdomen.

The lungs showed a bronchopneumonic area of the right base which appeared to be due to a terminal infarct. There was no embolus in the artery. The left lung was adherent to the pericardium.

The heart on examination showed marked dilatation of the left ventricle. The mitral valves were clear. On the edge of the aortic valves which were sterile on culture there were many old sclerotic verrucae. There were subendothelial markings and a marked adhesive pericarditis.

Libman, in discussing Sir Thomas Horder's paper on this subject at the 85th Annual Meeting of the British Medical Association,⁷ was led to believe from observations up to 1917 on a series of 109 cases, that 25 per cent of persons having an infection of the valves of the heart by an anhemolytic streptococcus spontaneously lose their infection and die of the after results. "We have no idea of how often the infection may occur without being clinically observed and complete recovery follow."

In a review of the postmortem findings in patients dying of subacute bacterial endocarditis, the pathology encountered in the heart and pericardium is of primary importance. Coombs¹⁰ found from the Bristol General Hospital postmortem records that among patients dying of rheumatism in the first decade 100 per cent showed pericardial lesions, in the second decade

83.3 per cent, in the third, 41.6 per cent, in the fourth, 23.0 per cent, after the age of forty, 26 per cent, and taking all together 53.0 per cent. A large number of autopsies in patients dying at or before the age of 16 years of



FIG 5 Subacute endocarditis of the aortic cusps

rheumatic carditis showed effusions of a measurable quantity in less than 10 per cent, the average volume of the effusion being between four and five ounces. The deduction made by Coombs was that fluid rarely collects in the

pericardium in the rheumatic heart in quantities sufficient to collect for instrumental evacuation. Coombs²⁵ previously, in speaking of the differences between rheumatic and infectious endocarditis, stated that the difference is very definite, that in subacute bacterial endocarditis the endocardium is much injured, the myocardium slightly and the pericardium not at all (Figures 6 and 7). Thayer⁵ found pericarditis in two of 25 cases which had come to postmortem, or 8 per cent. Camp and White,²⁶ in an analysis of 1729 autopsies at the Massachusetts General Hospital, found that pericardial effusion of more than 100 cubic centimeters was present in 126 cases, 7.2 per cent. This stresses the fairly frequent presence of pericardial effusion in small amounts, 94 had less than 250 cubic centimeters. In 80 cases of subacute bacterial endocarditis reported by Clawson and Bell,²⁷ pericarditis was found in 18, 22.5 per cent. The normal amount of pericardial fluid may vary, but its amount is never large. At autopsies performed a few hours after death, a few cubic centimeters of clear, light yellow serum are usually found in the pericardial sac.²⁸ Cunningham²⁹ states that the pericardial sac contains a little fluid.

In my cases reported here the following postmortem findings were noted

Hydropericardium	18
Pericarditis	13
Fibrous	9
Adhesive	4
Myocarditis, chronic fibrous	14
Endocarditis, old rheumatic lesions	29
Chordae tendineae	4
Mitral	17
Tricuspid	4
Aschoff bodies	2
Bracht-Wachter bodies	6
Both Aschoff and Bracht-Wachter bodies (case 2)	1
Pulmonary pathology	
Pleural effusion	8
Pleural adhesions	18
Pneumonia	21
Broncho	14
Lobar	7
Lung collapse	1
Embolus	2
Infarcts	8

Kidney pathology as noted in 33 cases was as follows

Acute glomerulitis	2
Acute and chronic nephritis	2
Vascular nephritis	1
Degenerative nephritis	1
Infarction	17
Emboic glomerular nephritis	6
Chronic focal glomerulitis	4

The spleen showed infarction in 27 cases. Infarction of the dome of the spleen may cause a pleuritis at the base of the left chest¹⁸, this may be the first complaint in a patient active and with no previous incapacitation, and be treated as such, without recognition of the serious nature of the disease, of which this is but a symptom.

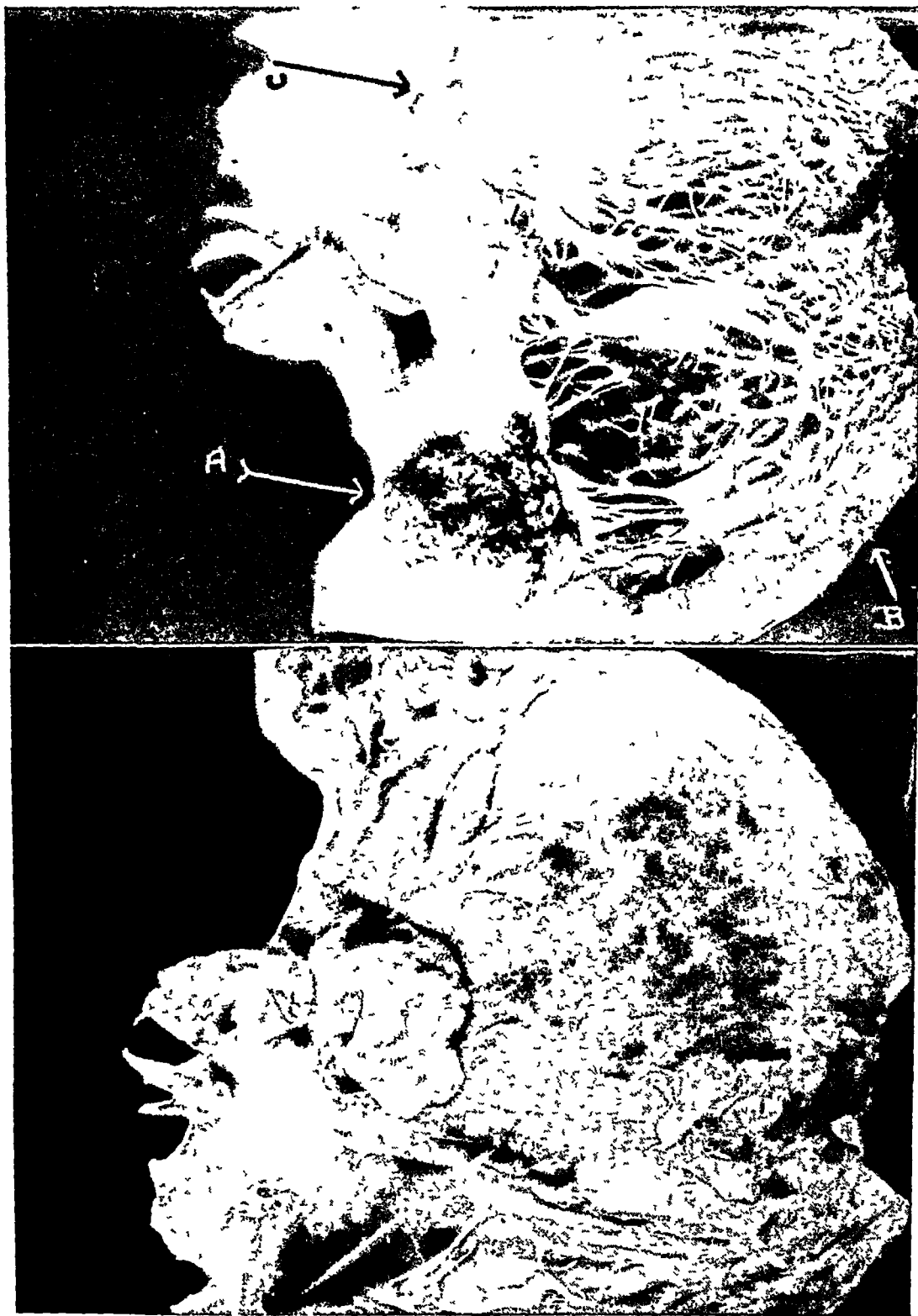


FIG 6 (above) (a) Subacute bacterial endocarditis of the mitral valve, *Streptococcus viridans* infection (b) Secondary intramural focus (c) Old rheumatic beading of the aortic and mitral valves

FIG 7 (below) The same patient as in figure 6 Marked adhesive pericarditis

Thrombus formation was distributed as follows

Right cerebral artery	1
Pulmonary artery	3
Iliac vein	2
Epicardial vessels	1
Common iliac artery	1
Renal artery	1

It has been stated that enlargement of the spleen is a common and early finding in bacterial endocarditis, this has not been true in my experience with this disease. An enlarged liver, often tender, has been encountered earlier than enlargement of the spleen. Nineteen patients had an enlarged liver on their first examination, 14 had an enlarged spleen, eight showed enlargement of both the liver and spleen on admission. This can readily be understood because of the function and physiology of the liver. On postmortem examination the spleen weighed over 200 grams in 30 of these cases. Infarction was present in 32, adhesions in one, congestion and edema in 22. In six cases, congestion and edema were the only findings. Six showed only postmortem changes. The liver at autopsy weighed over 1800 grams in 28 cases. Pathological changes were present in 45, these consisted of cloudy swelling and edema in 38, cloudy swelling alone in five, and chronic passive congestion alone in 17. Nutmeg liver was present in two as the only postmortem finding. Adhesions, liver scars, and acute hepatitis were each found once as the sole pathology present.

Petechiae were observed in 27 patients before death. Five of these patients also showed nodes of the toes, fingers or palmar surface.

Repeated examinations of the urine disclosed albumin in variable amounts in 26 patients, hyaline casts in 15, granular casts in nine, pus cells in 25, and red blood cells in 15.

Five of the 50 cases studied showed a positive Wassermann reaction before death, but none of these gave evidence on postmortem examination of syphilitic heart disease.

SUMMARY

Fifty consecutive postmortem examinations of patients coming under my observation have been analyzed to determine the relative frequency of the symptoms complained of, the age incidence (12 per cent being under 10 years of age), and the pathological changes found on postmortem examination. It was found that subacute bacterial endocarditis is not as uncommon in childhood as previously thought, that pericarditis in its various forms is compatible with a diagnosis of subacute bacterial endocarditis, that bacteremia and an enlarged tender liver are more characteristic early symptoms than manifestations of infarction or enlargement of the spleen. Although but 23 showed old healed rheumatic endocarditis, all showed evidence of some previous myocardial damage. There was no congenitally deformed heart in this group. Three had old healed vegetations together with active infectious verrucae at the time of death, and two had recovered from this disease only to succumb to its sequelae.

BIBLIOGRAPHY

- 1 COBURN, A F The factor of infection in the rheumatic state, 1931, Williams and Wilkins Co, Baltimore, p 59
- 2 BLUMER, G Subacute bacterial endocarditis, *Medicine*, 1923, ii, 103-173
- 3 SCHLIESINGER, B Subacute infective endocarditis in children, *Brit Jr Child Dis*, 1928, xxx, 23
- 4 ROST, W L, and FISCHER, A E Subacute bacterial endocarditis in childhood, report of twelve cases, *Am Jr Dis Child*, 1928, xxxvi, 1144-1160
- 5 THAYER, W S Studies in bacterial endocarditis, *Bull Johns Hopkins Hosp*, 1926, xxii, 4
- 6 LENHARTZ, H Ueber die septische Endocarditis, *München med Wehnschr*, 1901, xlviii, 1123-1178
- 7 HORDER, T J Infectious endocarditis, *Quart Jr Med*, Oxford, 1908-1909, ii, 289-324
- 8 LENHARTZ, H Die septischen Erkrankungen, *Nothnagel's specielle Path u Therap*, Wien, 1903, Bd iv, Theil iv, Abth 1
- 9 BLUMER, G A case of anthrax septicemia in a human being associated with acute anthrax endocarditis and peritonitis, *Bull Johns Hopkins Hosp*, 1895, vi, 127-132
- 10 COOMBS, C F Rheumatic heart disease, 1924, William Wood & Co, New York
- 11 PAGET, J An obstruction of the branches of the pulmonary artery, *Med Chir Trans*, 1844, xlviii, 162-188
- 12 LEWIS, T, and GRANT, R H Observations on subacute infective endocarditis, *Heart*, 1923, x, 121
- 13 ABBOTT, M E On the incidence of bacterial inflammatory processes on cardio-vascular defects and on malformed semilunar cusps, *Ann Clin Med*, 1926, iv, 189
- 14 PUSCHEL, E Fetal endocarditis, *Arch f Kinderh*, 1938, xiv, 1-11
- 15 FELDMAN, R Endocarditis in infants, *Jahrb f Kinderh*, 1937, cl, 138-156
- 16 MULSON, F W, and HESS, H R Acute rheumatic endocarditis in children, *Am Heart Jr*, 1936, xii, 368-369
- 17 STANSBY, J M, and LARSEN, L M Acute bacterial endocarditis in infancy, *Am Jr Dis Child*, 1930, xxxix, 1261
- 18 DENMAN, H C Subacute bacterial endocarditis, reports of six cases with autopsy findings, *Internat Clin*, 1932, ii, Series 42, 131-150
- 19 ABRAHAM, J Fetal endocarditis, *Zentralbl f Gynak*, 1937, lxi, 2698
- 20 LAWSON, G M, and PALMER, R S Occurrence of subacute bacterial endocarditis in childhood, *New England Jr Med*, 1928, cxcix, 1205
- 21 LEECH, C B *Streptococcus viridans* endocarditis in children, *Am Jr Med Sci*, 1930, clxxx, 621-628
- 22 LEVINE, S A Clinical heart disease, 1938, W B Saunders Co, Philadelphia
- 23 DENMAN, H C Unusual manifestations of *Streptococcus viridans* infection, *Internat Clin*, 1937, ii, Series 47, 15-21
- 24 LIBMAN, E Subacute bacterial endocarditis in the active and healing stages, *Practical Lectures*, 1925, Paul B Hoeber, Inc, New York, p 246
- 25 COOMBS, C F The microscopic or submiliary nodules of active rheumatic carditis, *Jr Path and Bact*, 1911, xv, 489
- 26 CAMP, P D, and WHITE, P D Pericardial effusion, a clinical study, *Am Jr Med Sci*, 1932, clxxxiv, 782-798
- 27 CLAWSON, B J, and BELL, C T A comparison of rheumatic and subacute bacterial endocarditis, *Arch Int Med*, 1926, xxxvii, 66-81
- 28 DELAFIELD, F, and PRUDEN, T M A text book of pathology, 1931, William Wood & Co, New York, p 603
- 29 CUNNINGHAM, D J Text book of anatomy, 6th Edition, Edited by A Robinson, 1931, Oxford Press, New York, p 886

PERIARTERITIS NODOSA: WITH CASE REPORTS *

By GEORGE M. JONES, JR., M. A., M. D., *Dallas, Texas*

A TOTAL of 101 cases of periarteritis nodosa reported in the English literature up to 1939 have been reviewed by Harris, Lynch and O'Hare¹. To date there have been a total of 14 pathologically proved cases in more than 460,000 admissions at the University Hospital of the University of Michigan. Three of these have previously been reported,^{2, 3} and the case histories of three others are to be published separately^{4, 5, 6}. The remaining cases are herein summarized for the purpose of adding further clinical information regarding periarteritis nodosa.

In addition to the above mentioned 14 cases a number of other closely allied diseases have been seen, including such conditions as dermato-neuro-angiomyositis, atypical periarteritis nodosa, a proliferative arterial intimitis with generalized arterial disease and multiple organizing thrombi, purulent periarterial lymphangitis and arteritis, questionable periarteritis nodosa, necrotizing arteritis and periarteritis of small vessels throughout the body as well as in the kidneys, in addition to the changes of advanced arteriosclerotic nephropathy. Clinically as well as pathologically, it is sometimes exceedingly difficult to draw a distinct line of demarcation between these various processes.

ETIOLOGY

The etiology of periarteritis nodosa is unknown. Syphilis has been proved to have no causal relationship. Of the three cases of this group that had positive Kahn reactions, two (Cases 5 and 11) were considered to be false positive reactions since there was no history or evidence of syphilis. Postmortem examination revealed no definite evidence of the disease in the third case (Case 2) nor in Case 11. The virus theory of etiology^{7, 8} has not been substantiated. The possible relationship of periarteritis nodosa to rheumatic fever cannot be disregarded^{9, 10, 11}. The association of periarteritis nodosa and vegetative endocarditis has been reported^{12, 13, 14}. Two of the University Hospital cases (Cases 4 and 7) had valvular endocarditis. Vining¹⁵ considers the possibility that the rheumatic infection in certain instances acts as the sensitizing factor and prepares the way for the destructive attack by the infective agent of periarteritis nodosa. Cohen, Kline and Young¹⁶ believe that periarteritis nodosa is a manifestation of clinical allergy so severe that irreversible and destructive lesions occur in the arterial walls and lead to disturbances in function of the organs supplied by the involved vessels. They consider every patient with severe allergy as a potential candidate for periarteritis nodosa. Other reports substantiate

* Received for publication May 16, 1941.

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor.

the frequency with which allergy is related^{17, 18, 19, 20} Harris, however, found allergy associated in periarteritis nodosa in only 15 per cent of the cases. Three patients presented in this report had an allergic history. Some claim periarteritis nodosa is not a disease sui generis but a hyperergic defensive reaction of the small muscular arteries and arterioles to a variety of toxic and infectious factors^{21, 22}. This belief receives support by the frequency with which preceding or concomitant infections are seen in cases of periarteritis nodosa. The most generally accepted opinion at present is that the disease results from sepsis and is a complicating or superimposed lesion which is not the primary event^{23, 24, 25}. Spiegel²⁶ points out that infection frequently precedes the onset of periarteritis nodosa within the course of a few months and suggests that an etiologic relationship exists between the two conditions. Ten of the 14 cases herein described were considered to be related to some infection, which included gonorrhea, abscess, bronchiectasis, prostatitis, and severe upper respiratory disorders. It should be noted that in another case not included in these 10 (Case 9) necropsy showed chronic cholecystitis, which might possibly have been related to the periarteritis nodosa. The case of periarteritis and arteritis of the temporal vessels from which *Staphylococcus aureus* was cultured by MacDonald and Moser²⁷ may have been pathologically similar to cases of purulent periarterial lymphangitis and arteritis seen in other patients at the University Hospital but differing from periarteritis nodosa.

PATHOLOGICAL CHANGES

The protean nature of periarteritis nodosa can best be understood by realizing that it is a disease primarily of the arteries and one which affects secondarily the tissues or organs they supply²⁸. It is an inflammatory reaction characterized by occlusion of the lumen as a result of thickening of the arterial wall, principally the media, or by thrombus, aneurysm formation, or rupture of the artery with hemorrhage²⁹. Kussmaul and Maier³⁰ first described adequately the microscopic changes of the disease. Arkin³¹ mentioned four progressive stages of changes in the arterial walls. The pathological process has been so well presented elsewhere that no further attempt to describe it will be made. The organs usually involved, in order of their frequency, are kidneys, heart, liver, gastrointestinal tract, mesenteric artery, muscles, spleen, lungs, and the peripheral and central nervous system^{1, 31}. The arterial changes of periarteritis nodosa would probably be seen more often in the central and peripheral nervous system if routine post-mortem examinations included a thorough study of these tissues. Secondary changes in the involved tissues are most frequently inflammation about the arteries, stasis, anemia, hemorrhage, edema, atrophy, fibrosis, infarction, and necrosis, depending upon whether the occlusion of the supplying artery was abrupt or sudden.

The pathological picture of periarteritis nodosa differs from that of dermato-neuro-angiomyositis only in the size of the vessels involved. The former ordinarily affects the middle-sized arteries, whereas the latter involves the smaller arteries and arterioles, with no one distinct line of demarcation. It is of interest to note that biopsies reported in Cases 10 and 11 were suggestive of angiomyositis, however, necropsy on Case 11 showed the middle-sized arteries more diseased than suspected from the biopsy. It is easily conceivable that arteries of both sizes and arterioles may be involved in the same case.

Table 1 shows the organs in which the microscopic vascular changes of periarteritis nodosa were found at necropsy. Only specimens of the heart,

TABLE I
Organs in Which Microscopic Vascular Changes of Periarteritis Nodosa
Were Found on Postmortem Examination in Cases Reported

Case No	Kidneys	G I tract including mesenteric arteries	Reproductive organs	Pancreas	Heart	Liver	Gall-bladder	Adrenals	Central nervous system	Lungs	Spleen
1	+	+	+	+	+	+	0	0	+	0	0
2	+	+	+	+	+	+	0	+	0	0	0
3	+	+	+	+	+	0	+	+	+	0	0
4	+	+	+	+	+	+	0	0	0	0	0
6	+	+	+	+	+	+	+	0	0	+	+
7	+	+	+	+	+	0	+	+	0	0	0
9	+	+	+	0	+	+	0	0	0	0	0
11	+	+	+	+	0	0	+	+	+	0	0
13					0	0				+	0
Av	8/8 100%	8/8 100%	8/8 100%	7/8 88%	7/9 78%	5/9 54%	4/8 50%	4/8 50%	3/8 38%	2/9 22%	1/9 11%

liver, lungs, and spleen were sent to the pathologist in Case 13. In Case 5, examination of the gall-bladder after cholecystectomy revealed changes in the arteries characteristic of periarteritis nodosa. Muscle biopsies showed typical arterial changes in five cases ante mortem, although in Case 3 biopsies failed to demonstrate periarteritis nodosa. It must be remembered that more widespread involvement than is indicated here would likely be found if it were possible to examine each entire organ microscopically. Obviously many microscopic arterial changes are overlooked during routine postmortem examinations, and likewise many muscle biopsies may be reported as negative.

SIGNS AND SYMPTOMS

The signs and symptoms have been adequately reviewed by Harris, et al.¹ The 14 cases seen at the University Hospital are summarized in table 2. Cases 1, 2, and 4 were included in Harris' summary. Although the number of cases in the present series is obviously less than in Harris' group, it is felt that the percentages of symptoms listed are of significance since the entire

series reported is from the records of one hospital rather than a collection from reports in the literature which are not always complete in details. For instance, in the present series weakness was a symptom in 93 per cent of the cases, whereas Harris' review shows it in only 41 per cent

TABLE II

A Summary of the Signs and Symptoms of Periarteritis Nodosa in the 14 Proved Cases Seen at the University Hospital

Case	Age	Sex	Race	Duration	Antemortem diagnosis	Previous or concomitant infection	Positive serology	History of allergy	Weakness	Fever	Tachycardia	Loss of weight	Hematuria	Dyspnea
1	46	M	W	7 mos					+		+	+	+	+
2	16	M	C	?16 mos		+	+		+			+	+	+
3	48	M	W	10 mos					+	+		+	+	+
4	47	M	W	11 mos	+	+		+	+	+	+	+	+	+
5	39	M	W	7 mos	+	+	?+		+	+	+	+	+	+
6	65	M	W	?		+		+	+	+	+	+	+	+
7	15	F	W	5 wks		+			+	+	+	+	+	+
8	51	F	W	17 mos	+	+		+	+	+	+	+	+	+
9	62	M	W	?					+	+	+	+	+	+
10	50	M	W	27 mos	+	+			+	+	+	+	+	
11	43	M	W	13 mos	+		+		+	+	+	+	+	
12	49	M	W	15+ mos	+	+			+	+	+	+	+	+
13	22	F	W	4 mos		+			+	+	+	+	+	+
14	36	M	W	4+ mos	+	+			+		+	+	+	+
Av	42	3F 11M	1C 13W	11 1 mos	7 50%	10 71%	3 21%	3 21%	13 93%	10 71%	11 78%	10 71%	10 71%	9 64%

TABLE II (Continued)

Case	Age	Sex	Race	Duration	Neuritis, including muscle aches	Albuminuria	Leukocytosis	Anemia	Arthritis-pain and/or swelling in joints	Abdominal pain	Edema	Emaciation	Cough	Nausea
1	46	M	W	7 mos	+	+	+		+	+		+	+	
2	16	M	C	?16 mos					+					+
3	48	M	W	10 mos	+	+	+	+	+	+	+	+		+
4	47	M	W	11 mos	+		+	+	+	+	+	+	+	+
5	39	M	W	7 mos	+	+	+	+	+	+	+	+	+	+
6	65	M	W	?	+				+	+	+	+	+	+
7	15	F	W	5 wks				+	+	+			+	+
8	51	F	W	17 mos		+	+	+	+	+		+		
9	62	M	W	?		+	+	+	+		+		+	+
10	50	M	W	27 mos	+	+	+	+			+	+		
11	43	M	W	13 mos	+		+	+	+	+	+			
12	49	M	W	15+ mos	+	+				+			+	
13	22	F	W	4 mos			+						+	
14	36	M	W	4+ mos	+	+	+			+	+	+		+
Av	42	3F 11M	1C 13W	11 1 mos	9 64%	9 64%	9 64%	8 57%	8 57%	8 57%	8 57%	8 57%	7 50%	8 57%

TABLE II (Continued)

Case	Age	Sex	Race	Duration	Rapid onset	Hypertension	Headache	Atrophy	Uremia	Coma	Palpitation	Hematemesis or bloody stools	Eosinophilia	Sensory involvement
1	46	M	W	7 mos		+			+					+
2	16	M	C	?16 mos	?+		+		?+	+				+
3	48	M	W	10 mos	+	+	+	+			+	+	8% 63- 77%	+
4	47	M	W	11 mos				+						
5	39	M	W	7 mos		+		+	+	+		+		
6	65	M	W	?		+	+	+	+	+	+	+	4%	+
7	15	F	W	5 wks	+						+	+	4%	
8	51	F	W	17 mos					+				20- 23%	
9	62	M	W	?		+	+			+		+		
10	50	M	W	27 mos	+	+		+	+	+			1- 28%	+
11	43	M	W	13 mos			+							+
12	49	M	W	15+ mos	+		+	+			+		3- 8%	
13	22	F	W	4 mos	+						+			
14	36	M	W	4+ mos	+	+	+	+				+		
Av	42	3F 11M	1C 13W	11 1 mos	7 50%	7 50%	7 50%	7 50%	6 43%	5 36%	5 36%	6 43%	5 36%	5 36%

TABLE II (Continued)

Case	Age	Sex	Race	Duration	Vomiting	Visual disturbances	Icterus	Purpura or other skin changes	Cyanosis	Nocturia	Pain or pressure in chest	Vertigo	Convulsions	Nodules
1	46	M	W	7 mos			+			+	+			
2	16	M	C	?16 mos	+					+			+	
3	48	M	W	10 mos	+	+	+	+	+	+				
4	47	M	W	11 mos				+						
5	39	M	W	7 mos	+									
6	65	M	W	?					+					
7	15	F	W	5 wks	+	+	+	+						
8	51	F	W	17 mos		+								+
9	62	M	W	?					+					
10	50	M	W	27 mos										
11	13	M	W	13 mos		+				+		+		
12	49	M	W	15+ mos			+							
13	22	F	W	1 mos							+	+		
14	36	M	W	4+ mos	+	+				+				+
Av	42	3F 11M	1C 13W	11 1 mos	5 36%	5 36%	4 28%	3 21%	3 21%	4 28%	2 14%	2 14%	1 7%	2 14%

Pain or swelling of joints or both was a complaint in a surprisingly large number (57 per cent) of the present review, but in the previous study it occurred in only 27 per cent of the patients. Of course, one could not defi-

nitely say that the joint symptoms were due to periarteritis nodosa in all instances, only one of which (Case 7) showed objective signs of joint involvement. Eight of the patients of the present series had some nausea during their illness, although this was previously reported in only 17 per cent of the cases. Other symptoms with higher percentages in the present series are weight loss, neuritis, hematuria, dyspnea, emaciation, cough, atrophy, icterus, and headache. A comparison of the frequency of signs and symptoms as recorded by Harris and as seen in the present series is shown in table 3.

TABLE III

A Comparison of the Frequency of Signs and Symptoms of Periarteritis Nodosa as Recorded by Harris and as Seen in the Proved Cases at the University Hospital

	Harris %	Univ Hosp %		Harris %	Univ Hosp %
Weakness	41	93	Headache	29	50
Tachycardia		78	Atrophy	25	50
Fever	80	71	Uremia		43
Loss of weight	48	71	Hematemesis or bloody stools		43
Hematuria	47	71	Coma		36
Dyspnea	41	64	Palpitation		36
Neuritis	48	64	Eosinophilia	19	36
Albuminuria	65	64	Sensory involvement	31	36
Leukocytosis	70	64	Vomiting	31	36
Anemia		57	Visual disturbances	23	36
Arthritis	27	57	Icterus	12	28
Abdominal pain	57	57	Nocturia		28
Edema	52	57	Purpura or other skin changes	22	21
Emaciation	36	57	Cyanosis	21	21
Nausea	17	57	Pain in chest	16	14
Cough	36	50	Vertigo	8	14
Rapid onset	58	50	Nodules	16	14
Hypertension	46	50	Convulsions	15	7

The ratio of 11 males to three females in the group now reported coincides with the previous report of three to one. The average age of 42 years was slightly higher than the previously reported average of 36.9 years. The average duration of the illness of 11.1 months is longer than that of 8.6 months previously reported. The duration of illness in Cases 6 and 9 could not be accurately estimated on account of the history of known high blood pressure for three and five years respectively and because of the possibility of all symptoms being due to the hypertension. If the hypertension in these cases was due to periarteritis nodosa, the disease of necessity would be of longer duration than previous average estimates. Among the constitutional symptoms, weakness was the most common. Leishman²³ lists it as one of the common symptoms. Tachycardia and fever were present in 11 and 10 cases, respectively. The fever is usually low-grade, below 101°, although in Case 10 it rose to as high as 104°. Boyd and Nussbaum²¹ point out that tachycardia disproportionately rapid for the body temperature is suggestive of periarteritis nodosa. Weight loss, in some cases exceeding 50 pounds,

was present in 10 of the cases, or 71 per cent. Leukocytosis is common, and a significant eosinophilia (8 per cent or higher) was seen in five of the 14 cases. Eight of the patients had anemia. Emaciation and atrophy are frequently observed. The onset of the illness was considered acute in six, and questionably so in a seventh case.

Among the cardio-respiratory symptoms, in addition to the tachycardia, are dyspnea, palpitation, cough, edema, and a feeling of pain or pressure in the chest. It is interesting to note that Case 13, without cardiac involvement, had all these symptoms except edema. The periarteritis nodosa in this case affected the pulmonary vessels. With the vessels of the heart diseased as frequently as they are, one would expect cardio-respiratory symptoms to occur frequently.

Signs of gastrointestinal tract involvement included abdominal pain, nausea, and vomiting. These were considered serious enough in Case 5 to warrant laparotomy and cholecystectomy, without which the antemortem diagnosis would not have been made. Not only cholecystectomy but also appendectomy and nephrectomy have been performed as a result of mistaken antemortem diagnoses^{26, 32, 34, 35}. Several instances of intra-abdominal aneurysm with perforation and resultant symptoms have been reported^{34, 35, 36}. Six of the 14 patients presented here had gastrointestinal hemorrhage as evidenced by hematemesis or the presence of blood in the stools. Pass³⁹ found only 52 cases of anemic infarction of the liver reported in the English literature up to 1935, periarteritis nodosa was the most common cause of the condition. A few other cases have been reported since⁴⁰. Arkin's Case 5 showed "hepar lobatum" believed to be caused by periarteritis nodosa. Case 6 of this group showed a healed infarct of the liver on postmortem examination. Four cases of the present series had some icterus, most marked (Case 12) when an associated enlargement of the liver was present. The jaundice later disappeared, and the liver receded in size. It seems probable that this patient had a single large infarct or multiple small ones. In two cases (Cases 7 and 8) the spleen was palpable,⁴⁷ although in only one case (Case 6) were the arteries of this viscus found involved. Middleton and McCarter¹¹ presented a case with a glucose tolerance test interpreted as diabetic in which postmortem examination showed periarteritis nodosa involving the pancreas. The glucose tolerance test in Case 10 was of the diabetic type.

Signs and symptoms referable to the genito-urinary tract are frequent. Among the evidences of kidney damage observed are hypertension, hematuria, albuminuria, nocturia, edema, uremia, and coma. Casts are frequently present in the urine. Five of the cases presented here and questionably a sixth had uremia, and five became comatose prior to death. It is interesting to note that in addition to Cases 6 and 9 with typical histories of essential hypertension and no symptoms suggestive of other complications, several similar cases have been seen in which necropsy revealed a questionable periarteritis nodosa, but not sufficiently definite to be included in this

report Only time will tell whether the last blood pressure recording of 148 mm Hg systolic and 94 mm diastolic in Case 12 is an indication of developing hypertension Keegan³² reports a case in which a right nephrectomy was performed and the kidney showed periarteritis nodosa The patient died two months later, at which time the other kidney had the changes of early arteriosclerosis and chronic vascular nephritis He postulated that many cases of chronic vascular nephritis may have their origin in mild renal periarteritis nodosa This seems quite possible and may be substantiated by the finding of both periarteritis nodosa and arterio- and arteriosclerotic nephropathy in a number of cases on postmortem examination (Cases 6 and 9) The diagnosis in Case 14 was definitely established only after splanchnicectomy for a supposed malignant hypertension The frequency of genito-urinary tract symptoms is easily understood when one realizes the frequency of involvement not only of the kidneys but also of various organs of reproduction, including the testes, seminal vesicles, prostate, epididymes, salpinges, and ovaries The testicular pain reported in Case 12 was most likely on the basis of disease of the vessels of the testes

Nervous system involvement may be indicated by headache, neuritis, muscular atrophy, sensory changes in the form of anesthasias and paresthasias, visual disturbances, vertigo, and convulsions Neuritis, including muscle aches, was present in nine cases The most completely studied case in the English literature showing sensory changes during the course of periarteritis nodosa is that of Fitz, Parks, and Branch³⁷ Eyeground changes, as those in Case 3, have been previously reported with examinations showing periarteritis nodosa of the vessels of the eye^{12, 25, 38} Bernstein³⁸ reports a case of progressive nerve deafness of periarteritis nodosa origin The deafness in Case 10 seems to be another such case

Skin lesions in periarteritis nodosa have been quite varied One of the most interesting examples is the case in which the diagnosis during life was disseminated lupus erythematosus but the necropsy showed periarteritis nodosa⁴² An erythematous eruption appeared in Case 3 Dunbar⁴¹ presented a case of periarteritis nodosa with associated thrombocytopenic purpura Case 7 had purpura hemorrhagica Several cases of gangrene and ulceration on the extremities have been reported^{13, 14} Case 4 had an ulcerated elbow Subcutaneous nodules, previously considered as diagnostic of the disease, occurred in only two cases (Cases 8 and 14)

TREATMENT

One must conclude, with Harris, et al, that there is no specific treatment for periarteritis nodosa Cases 2 and 4 received adequate neoarsphenamine therapy without benefit^{44, 45} Case 10 remained afebrile while receiving sulfanilamide, and had the longest duration of disease of the cases reported He was afebrile, however, for five days before taking the drug Case 12 took small doses of sulfanilamide and is still alive, but this could not pos-

sibly be attributed to the drug. Case 11 was given adequate treatment with sulfanilamide and died 13 months after the onset of symptoms. Since there is no known treatment and there is so often an associated infection, it seems justifiable to give sulfanilamide or sulfapyridine until an adequate number of cases have been accumulated from which conclusions may be drawn.

PROGNOSIS

Twelve of the 14 patients in the present series are dead, although five left the hospital alive. Two recent cases reported³⁷ indicate a duration of life of eight and six years after the onset of symptoms. These would raise Harris'¹ average duration of illness considerably. The longest duration of the disease actually reported is 12 years.⁴⁶ Such reports of longevity of patients with the disease are rare. The longest known duration of life of the 14 cases reported here is 27 months (Case 10). Case 7 apparently lived only five weeks after the onset of symptoms caused by periarteritis nodosa. One must conclude that the prognosis is extremely poor, although Case 12 is alive and nearly asymptomatic at the present time, and Case 14 is living. It is conceivable that mild cases may remain undiagnosed and live considerably longer than present reports indicate.

SUMMARY AND CONCLUSIONS

To date 14 proved cases of periarteritis nodosa have been observed at the University Hospital. Their signs and symptoms have been summarized. Seven of the 14 cases had antemortem diagnoses of periarteritis nodosa. Such a diagnosis can be proved only by positive biopsy report, although negative biopsy reports do not rule out the diagnosis.

The symptoms are varied as arteries in any portion of the body may be involved. The most common symptoms are referable to the organs most commonly affected.

The duration of the illness is closely correlated with the degree of involvement of the vital organs and resultant impairment of function of those organs. The average length of life after the onset of illness in this group of cases was 11.1 months.

Although the etiology of periarteritis nodosa is unknown, the close relationship between the disease and previous and concomitant infections is noted.

There is no specific treatment. The prognosis is poor. Only two of the 14 cases of this series are alive at the time of writing.

CASE REPORTS

Case 1. J. B., admitted on October 9, 1930, was previously reported by Hauser. Outstanding features of this case were epigastric pain, weakness, loss of weight, joint pains, paresthesia, hypertension, pain in the right side of the chest, dyspnea,

albuminuria, and uremia. Autemortem diagnosis was chronic glomerulo-nephritis but postmortem examination showed diffuse periarteritis nodosa.

Case 2. J. L. B., observed on September 1, 1931, was also previously reported by Hauser.² The outstanding features were swelling and pain in the right side of the face, headache, vomiting, ulceration of nasopharynx, convulsion, and coma. The patient had a positive blood Kahn reaction. Autemortem diagnoses had been tertiary syphilis and luetic osteomyelitis of the maxillae and palate. He had received intensive bismuth and arsphenamine antiluetic therapy. Necropsy showed periarteritis nodosa but no evidence of syphilis.

Case 3. J. F., a 48-year-old white male, was first admitted to the hospital on August 1, 1932, with a history of nausea, vomiting, chills, fever, and night sweats occurring on December 25, 1931, after an alcoholic debauch, with the onset of pain in the calves of his legs three days later. Shortly afterward he had difficulty in walking, a staggering gait, and numbness and tingling of the toes and feet. In April, 1932 he noted swelling of his feet and ankles, palpitation, dyspnea, and nocturia. Prior to admission to the hospital, some friends observed that he was jaundiced. At the age of 19 years he had had gonorrhea and a "soft chancre" for which some "arm injections" were given although he was not told that he had syphilis. There was a brown ulcerating lesion on his neck for one year.

Physical examination revealed a well developed, well nourished adult white male, not acutely ill, but with slightly icteric skin. Temperature was 100°, pulse 84 per minute, respirations normal, and blood pressure 190 mm Hg systolic and 112 mm diastolic. There was a brown ulcerated lesion on the neck. The heart was enlarged to 11 cm to the left of the midsternal line. A systolic murmur was present at the apex. Rales were heard in the left posterior midscapular region. The radial arteries were tortuous but not beaded. There was pitting edema of the feet and ankles. The Achilles jerk was absent bilaterally, and plantar stimulation caused no flexion on either side. Gait was slow and ataxic.

The blood Kahn reaction was negative. The spinal fluid Kahn reaction was also negative, total spinal fluid protein was increased to 79 mg per 100 c c, and the globulin was 3 plus. The colloidal gold curve was 0011100000, and mastic curve was 221100. The spinal fluid was clear with no cells present. Urinalyses showed an occasional trace of albumin and a rare red blood cell. The hemoglobin was 80 per cent with white blood cell counts ranging from 10,800 to 14,000 per cubic millimeter. The differential counts were normal except for an 8 per cent eosinophilia on two occasions. The renal function tests were normal. The blood non-protein nitrogen, the basal metabolic rate, and agglutinations for the typhoid-dysentery-brucella groups were also normal. The blood culture was negative. The electrocardiogram showed slightly inverted T-waves in Lead II, sharply inverted T-waves in Lead III, and small Q-waves in all leads. Chest roentgen-ray showed elongation of the aorta and increased peritruncal markings. Gastrocnemius biopsy report was "marked degenerative changes in the voluntary muscle. Zenker's necrosis. Interstitial myositis, but no significant eosinophilia in the infiltrations. This is a degenerative myositis of some unknown etiology. No trichinosis" (Dr. C. V. Weller). Biopsy of the deltoid muscle revealed nothing abnormal. Pathological report on the lesion removed from the neck was "squamous cell carcinoma of the mediocellular type. Ulcerating secondarily infected surface" (Dr. C. V. Weller).

While in the hospital there were daily temperature elevations often as high as 101 degrees. The pulse averaged 85 per minute. The slightly icteric tint disappeared. Ophthalmoscopic examination showed arteriosclerosis of the retinal vessels with a few small retinal hemorrhages. Roentgen-ray therapy was applied to the site of removal of the carcinoma of the neck. His condition was reported as somewhat improved when he was discharged on July 15, 1932 with final diagnoses of essential hypertension,

fever of unexplained etiology, peripheral polyneuritis, interstitial myositis, and carcinoma of the neck

He was readmitted on October 18, 1932 with the interval history of slight diminution of previous symptoms but with recent fatigue, epigastric distress, blurring of vision, temporal and occipital headaches, loss of 50 pounds in weight, weakness, wasting of arms and legs, and stinging sensations in the balls of the feet and toes

Physical examination then revealed an emaciated male with marked muscular atrophy. Blood pressure was 240 mm Hg systolic and 150 mm diastolic. There was an erythematous eruption over the lower portion of the chest and upper abdomen. Ophthalmoscopic examination showed advanced albuminuric retinitis with numerous hemorrhagic areas. There was diminution of the senses of touch, position, pain, and temperature below the knees. Otherwise, findings were essentially the same as on the previous admission.

The spinal fluid Kahn reaction remained negative, the globulin was 4+, the colloidal gold curve was 4234311000, and the mastic 332210. The spinal fluid was clear with about 10 red blood cells per cubic millimeter. The spinal fluid pressure was normal. Urinalysis showed a one plus albuminuria with a few red cells and occasional hyalin and granular casts. Blood examination revealed a hemoglobin of 68 per cent and a white blood cell count of 14,000 per cubic millimeter with a normal differential count. Gastric analysis showed a slight amount of hydrochloric acid. The blood non-protein nitrogen was normal on October 20. Roentgen-rays showed a normal upper gastrointestinal tract and a moderate generalized osteoporosis.

During the hospital course, the patient's condition became worse, with persistent epigastric distress, hiccoughing, and a dark brown hematemesis on October 31, followed by bilateral râles, increasing dyspnea, and cyanosis. Respirations ceased on November 1, 1932. In addition to the previous diagnoses a metastatic neoplasm was strongly suspected.

Necropsy disclosed periarteritis nodosa involving the arteries of the brain, heart, trachea, entire gastrointestinal tract, pancreas, gall-bladder, adrenals, kidneys (old ruptured aneurysm in one branch of renal artery), testes, seminal vesicles, and within the nerve bundle of the left common peroneal nerve, generalized arteriosclerosis, old area of softening in the basal ganglia, localized renal atrophy, marked left ventricular hypertrophy and terminal cardiac failure with right-sided dilatation, early purulent bronchitis and bronchopneumonia, diffuse fibrous atrophy of right testis, scattered subserous and submucosal petechial hemorrhages, passive congestion and parenchymatous degeneration of all organs, no metastatic lesions (Dr B M Hathaway)

Case 4 E R, admitted on August 17, 1932, has previously been reported by Curtis and Coffey.³ The outstanding features of this case were pain in the arms and legs, anorexia, loss of weight, nausea, weakness, generalized atrophy, edema of the hands and feet, secondary anemia, leukocytosis, and eosinophilia as high as 77 per cent. The diagnosis in this case was recognized prior to necropsy.

Case 5 R H, a 39-year-old white male, entered the hospital on January 6, 1934, with a history of a loss of 54 pounds in weight, loss of strength, and a constant abdominal ache. In July 1933, he had had a polyarticular arthritis with swollen, painful joints for one month, edema of the legs, and enlargement of the liver. All of his teeth had been extracted. His symptoms disappeared until November, 1933, when he was chilled on a hunting trip. Two days later a dull, persistent generalized abdominal ache appeared which was not related to meals. He became constipated, and five weeks prior to admission developed an intermittent, low-grade fever. There was no history of primary or secondary syphilis. He had previously been in good health.

Physical examination revealed a well developed, poorly nourished white male with normal facial flush, and sunken cheeks. Temperature was 100.4°, pulse, 90 per

minute, respirations, 20 per minute, and blood pressure, 150 mm Hg systolic and 96 mm diastolic. The patient was edentulous and had a post-nasal discharge. There was a soft systolic apical murmur. The pulse was forceful, and the second aortic valve sound was loud. Lungs were normal. The recti muscles were quite tense, especially in the upper abdomen which made thorough abdominal examination impossible. There did not appear to be any abdominal tenderness. There was marked atrophy of the extremities with muscle tenderness. Costovertebral angle tenderness was present bilaterally. The prostate was tender but otherwise normal.

One Kahn reaction was two plus positive, one was one plus positive, and two were negative. Several urinalyses prior to January 31 were negative except for a rare red blood cell. After that date, however, urinalyses on a number of occasions showed a two plus albuminuria with occasional granular casts and red cells. The hemoglobin was 75 per cent. White blood cell count varied from 11,940 to 26,300 per cubic millimeter with normal differential counts, which did not show at any time more than 2 per cent eosinophiles. Blood culture was negative. Blood bilirubin was 2.5 milligrams per 1,000 c.c. (indirect). Between January 26 and February 12, the blood non-protein nitrogen rose from 38.2 to 114.5 milligrams per 100 c.c. Electrocardiogram was normal. Prostatic smear contained innumerable pus cells, although the patient gave no history of infection. Roentgen-ray examinations showed faint visualization of a distended gall-bladder, an enlarged liver, and normal chest, upper gastrointestinal tract, and colon.

As the gall-bladder showed only faint visualization and was distended enough to reach the right iliac crest, and since no other diagnosis was established, this patient had an exploratory laparotomy and cholecystectomy on January 15. At this time the liver was found somewhat hard but no other abnormality was noticed. The report of the pathologist following cholecystectomy was "No cholecystitis in the ordinary sense. Many of the medium-sized arteries show various stages of medial necrosis and productive as well as exudative periarteritis. This patient probably has a systemic arterial disease, belonging in the general group of periarteritis nodosa" (Dr. C. V. Weller). The wound was well healed by January 27. The temperature rose as high as 102.4° during the hospital course, with the pulse ranging between 84 and 122 per minute. The patient's symptoms continued and consisted chiefly of pains in the back of his neck and in his extremities. On some occasions he vomited material which contained fresh blood. He became irrational on February 9 and semi-comatose on February 10, respirations became Cheyne-Stokes in type. He was removed from the hospital against advice on February 12, with final diagnoses of periarteritis nodosa, subacute nephritis, hypertension, uremia, secondary anemia, and chronic prostatitis. Death occurred outside the hospital on February 22, 1934. No necropsy was performed.

Case 6 E. A., a 65-year-old white male, entered the hospital on August 22, 1934, with the chief complaints of shortness of breath and swelling of the feet and ankles. He had suffered from mild asthmatic attacks for 25 years. Fourteen years ago he had been told he had heart trouble, and three years ago it was discovered that he had hypertension. He had been asymptomatic, however, until the winter prior to admission when he observed dyspnea on slight exertion, headaches, weakness, cough productive of sputum, sometimes bloody, and weight loss. For the last few weeks he had noticed occasional "fluttering" in his heart, and one week prior to admission he first became aware of swelling of his feet and ankles. For 10 weeks he had experienced a severe diarrhea with frequent stools which were sometimes bloody, with gaseous distention and nausea. There was a history of gonorrhea 25 years previously with several exacerbations since. Owing to the patient's confused mental condition it was not possible to obtain a more reliable history.

Physical examination revealed a poorly nourished, dehydrated, elderly white male, quite dyspneic at bed rest. Temperature was 98°, respirations, 30 per minute, and

blood pressure, 150 mm Hg systolic and 110 mm diastolic. The skin was dry, deeply pigmented, and parchment-like. The lips were slightly cyanotic. The teeth were in extremely poor condition with root fragments remaining. There was engorgement of the cervical veins. The thorax was emphysematous, and there were numerous musical râles throughout both lung fields with a prolonged expiratory phase. Inconstant râles could be heard in both lung bases. The left border of cardiac dullness was 14 cm to the left of the midsternal line. There was auricular fibrillation with a pulse deficit, the apex rate being 114 per minute and the radial pulse 78 per minute. A loud, harsh, systolic murmur was heard best at the apex. The peripheral vessels were markedly sclerotic. The firm, slightly tender liver edge extended to the umbilicus. Moderate edema of the ankles was present. All reflexes were diminished, and there was diminution in sensation over the right forearm. The muscles showed extensive atrophy.

The Kahn reaction was negative. The blood examination showed 90 per cent hemoglobin and a white blood cell count of 8,200 per cubic millimeter with normal differential, showing 4 per cent eosinophiles. A one plus albuminuria was present and the urinary sediment showed 2 to 3 red blood cells and 2 to 3 white blood cells per high power field. The stool examination revealed a three plus guaiac reaction. The blood non-protein nitrogen was 55.5 mg per 100 c.c.

The patient was given two injections of 0.016 gm morphine sulfate during the first eight hours of hospitalization. Eleven hours after admission respirations had dropped to 5 to 8 per minute. Digifolin was administered intravenously and digitalis was given by mouth. Several doses of caffeine sodio-benzoate were injected. He became comatose and cyanotic with labored respirations. His course was progressively downhill and he died 33 hours after admission to the hospital. Antemortem diagnoses were arteriosclerotic and hypertensive heart disease with auricular fibrillation and cardiac enlargement, cerebral arteriosclerosis, bronchial asthma, pulmonary emphysema, and hypertrophic arthritis of the spine.

Necropsy showed periarteritis nodosa involving the coronary, pulmonary, bronchial, diaphragmatic, splenic, mesenteric, pancreatic, hepatic, cholecystic, renal, testicular, prostatic, and other arteries, multiple healed myocardial infarcts, old sclerosing epicarditis, hydropericardium, bilateral hydrothorax, ascites, acute exacerbation of chronic passive congestion of all organs, acute pulmonary edema, old healed pulmonary tuberculosis and adhesive pleuritis, generalized arteriosclerosis, arterio- and arteriolo-sclerotic nephropathy, fibroid atrophy of the testes, healed infarct of liver, old leptomeningeal thickening (no periarteritis nodosa of meningeal, spinal, or cerebral arteries). (Dr J. C. Bugher)

Case 7. L. W., a 15-year-old white female, was admitted on August 13, 1935, with chief complaints of weakness and cough. Since she had whooping cough at the age of 9 months, there had been a cough productive of small amounts of sputum which was never bloody. The cough had been worse for the last four or five years, but otherwise the patient had felt well. About five weeks prior to admission she developed pain in both ankles without swelling or redness. This spread to the knees, right shoulder, little finger of the right hand, and index and ring fingers of the left hand. For four weeks she had had some fever, easy fatigability, palpitation, and shortness of breath on mild exertion. Pallor became pronounced, and the patient had a more productive cough with blood-streaked sputum. Recently she had complained of sore throat and soreness of the tongue. For the last week or so the patient had complained of dull left upper quadrant pain which radiated across the abdomen. There had been ecchymosis and swelling of the right eye for one day.

Physical examination revealed a strikingly dyspneic adolescent female who appeared acutely ill with pallor and a yellowish tinge. The temperature was 101.8°, pulse 138 per minute, respirations 38 per minute, and blood pressure, 118 mm Hg.

systolic and 40 mm diastolic. There was an area of ecchymosis and swelling of the upper and lower eyelids on the right. In the left axilla was a small area with crusted blood. The patient had a slight mucopurulent nasal discharge. The post-pharyngeal wall was reddened. The breath sounds were harsh with a few coarse rhonchi on coughing. The lungs were otherwise normal. The left border of cardiac dullness was 10 cm to the left of the midsternal line. A systolic murmur was heard at the apex, and the apex beat was forceful. The spleen was palpable just below the left costal margin. There was clubbing of the fingers and toes, with fusiform swelling of the interphalangeal joints of the right fifth and left second and fourth fingers, and periarticular swelling of the knees. The reflexes of the lower extremities were diminished bilaterally. Numerous hypertrophic papular crusted lesions were present over both elbows and the medial aspects of both knees.

The Kahn reaction was negative. Blood culture showed no growth. Hemoglobin was 30 per cent, red blood cell count was 1,750,000 per cubic millimeter, white blood cell count was 8,900 per cubic millimeter with a normal differential count. Two sputum examinations were negative for tubercle bacilli. The electrocardiogram was not definitely abnormal aside from a tachycardia of 120 per minute. No urinalysis was recorded. Chest roentgen-ray showed an acute exudative bilateral pulmonary lesion, conglomerate in certain areas without marked pleural reaction, with one calcareous peribronchial node at the right hilum, considered strongly suggestive of diffuse active tuberculosis.

The patient was given a blood transfusion and treated symptomatically. Her condition became worse, and about 30 hours after hospital admission she had a coughing spell, vomited a small amount of blood, had a small pulmonary hemorrhage, and respirations ceased. Antemortem diagnoses were probable subacute bacterial endocarditis, bilateral bronchiectasis and lung abscesses, infectious arthritis, septicemia, and secondary anemia.

Necropsy revealed generalized arterial disease, periarteritis nodosa of arteries of the pancreas, gall-bladder, adrenals, kidneys, fallopian tubes, heart and elsewhere in the body, late subacute glomerulonephritis, acute aortic valvular endocarditis, acute necrotizing laryngitis and tracheitis, chronic fibrocaceous bronchitis and peribronchitis, old fibrocaceous tuberculosis of bronchial nodes, cylindrical bronchiectasis, subacute ulcerative jejunitis (tuberculous?), multiple hemorrhages in lungs, petechial hemorrhages in skin, conjunctiva, gastrointestinal mucosa, and beneath peritoneum and pericardium, purpura hemorrhagica; terminal acute purulent lobular pneumonia, acute passive congestion of all organs, terminal right-sided cardiac dilatation with relative tricuspid insufficiency, pulmonary edema, ascites, chronic adhesive perisplenitis, agonal dissemination of gas-forming organisms, chronic pulmonary osteoarthropathy (Dr C V Weller).

Case 8 A H, a 51-year-old white female, was admitted to the hospital on October 14, 1935, with a history of having had the "grippe" and "congestion of the lungs" 16 months previously, with fever during the summer of 1934. She had since noticed weakness, and had developed an infection and swelling of the nose and suffered from a three-day attack of abdominal pain. Four months prior to admission there had been the onset of pain in the eyes, associated with redness. There had been a loss of 50 pounds in weight, shortness of breath, and swelling and soreness of ankles, knees, and hips. The patient had had asthma from the age of 3 to 13 years. Prior to admission to the hospital she had had an eosinophilia of 20 per cent and a muscle biopsy for suspected trichinosis. The biopsy was reported as showing periarteritis nodosa and the patient was sent to the hospital for substantiation of the diagnosis.

Physical examination showed a pale, malnourished, apparently chronically ill white woman with photophobia. Temperature was 99.6°, pulse, 100 per minute, respirations, 20 per minute, and blood pressure, 120 mm Hg systolic and 90 mm diastolic.

The breath was uriferous. There was circumcorneal conjunctival hyperemia with multiple small half-pinhead sized areas of infiltration of the conjunctiva. Heart and lungs were normal. The spleen was palpable on deep inspiration. There were "shot-sized" nodules over both elbows, red, non-tender, firm, and crusted at their surfaces.

The Kahn reaction was negative. Multiple urinalyses showed albuminuria, red blood cells, and white blood cells. The hemoglobin was 55 per cent, white blood cell count 11,700 per cubic millimeter, and 14,500 on two occasions with 20 per cent and 23 per cent eosinophilia, respectively. Stool examination was normal. Blood urea nitrogen was 60 mg per 100 cc, and the urea clearance test showed only 10.9 per cent and 9.6 per cent of normal function in the first two hours, respectively. The pathological report on the previously obtained muscle biopsy confirmed the previous pathological report of periarteritis nodosa. "The nutrient arteries and arterioles exhibit marked changes in various stages. There is necrosis of artery wall with a very marked periarterial inflammatory infiltration, polyblast formation, and fibroblastic reaction. In a somewhat later stage thrombosis occurs and this in turn is followed by organization. These are the changes of a primary disease of the smaller arteries closely resembling periarteritis nodosa as it occurs in arteries of a somewhat larger order" (Dr C V Weller).

The patient remained in the hospital until October 20, and was treated symptomatically. Her condition remained unchanged during the hospital stay. Pulse averaged 90 per minute and there was a low-grade afternoon fever to 100°. Final diagnoses were periarteritis nodosa, secondary anemia, splenomegaly, and eczematous keratoconjunctivitis.

Death occurred outside the hospital on November 16, 1935, according to her referring physician, with edema of the lungs and pneumonia.

Case 9 E M, a 62-year-old white male, entered the hospital on May 8, 1936, having had known high blood pressure with mild headaches for 5 or 6 years. In January, 1935, he had the onset of shortness of breath on exertion and ease of fatigue. The following October he observed the progressive development of orthopnea, edema of feet and ankles, cough, and weakness. One month prior to admission his hands began to swell, and he noticed one tarry stool six weeks previously. The patient's responses were not considered altogether reliable. He had been treated by his referring physician for arthritis.

Physical examination revealed a dyspneic and orthopneic, drowsy, acutely and chronically ill, elderly appearing, white male. Temperature was 99°, pulse, 102 per minute, respirations, 24 per minute, and blood pressure, 210 mm Hg systolic and 150 mm diastolic. There was cervical venous engorgement. Funduscopic examination showed arteriovenous nicking with generalized edema of the retina. Rales were heard in both lung bases. The heart was enlarged to 13 cm to the left of the midsternal line. There was a systolic precordial murmur. The heart sounds were distant. The peripheral vessels were sclerotic. The abdomen was enlarged, with shifting dullness, and there was pitting edema of the lower anterior abdominal wall, the scrotum, both lower extremities, and the hands. There was slight cyanosis of the nails.

The Kahn reaction was negative. Urinalysis showed a 4+ albuminuria with white blood cells, red blood cells, and finely and coarsely granular casts. Hemoglobin was 67 per cent and white blood count 6,400 per cubic millimeter with a normal differential count. Stool examination was normal. Blood non-protein nitrogen was 39.7 mg per 100 cc. Electrocardiogram on May 8 showed definite left axis deviation with T-waves slightly inverted in Lead I and on May 16, auricular fibrillation with A-V dissociation and ventricular extrasystoles causing perfect bigeminy, which suggested digitalis intoxication.

The patient was placed on a neutral diet with ammonium chloride and mercupurine, digitalis, morphine sulfate, and aminophyllin with loss of 15 pounds of edema.

in six days, after which he developed increased weakness and drowsiness. Death occurred on May 16, 1936. Temperature had varied from normal to 101° , and pulse from 66 to 114, averaging 90 per minute. The clinical diagnoses were essential hypertension, generalized arteriosclerosis, hypertensive and arteriosclerotic heart disease with congestive failure, and secondary nephritis.

Necropsy showed systemic arterial disease, periarteritis nodosa, involving chiefly the liver, the retroperitoneal tissues, intestine, and epididymis, with one small subepicardial vessel which showed a nodular eccentric perivascular proliferation, generalized arteriosclerosis, old anemic infarction of brain, arterio- and arteriosclerotic nephropathy, cardiac hypertrophy, most marked in the left ventricle, subendocardial fatty infiltration, terminal cardiac dilatation, nutmeg liver, chronic passive congestion of lungs, anasarca, ascites, hydropericardium, chronic cholecystitis and cholelithiasis. (Dr C V Weller)

Case 10 T K, a 50-year-old white male, was admitted to the hospital on February 21, 1938, with the chief complaint of numbness and tingling of the legs and feet. About five months prior to admission, he first noticed a burning type of pain in his feet which spread to his legs and knees, followed by difficulty in walking, weakness, numbness, and tingling. There was a weight loss of 33 pounds and fever almost daily. As long as the patient remained at rest the pains disappeared. The patient had been impotent for four to six months.

Physical examination revealed a well developed white adult male showing signs of weight loss and generalized muscular atrophy. Temperature was 101° , pulse, 108 per minute, respirations, 20 per minute, and blood pressure, 102 mm Hg systolic and 60 mm diastolic. There was slight pitting edema of the ankles. Vibration sense was diminished at the ankles, and there was mild hypalgesia over both feet. Moderate pallor of the mucous membranes was present. Râles were heard in the left posterior lung field. The left testicle was atrophied, and the right was small and soft.

The Kahn reaction was negative. Of five urinalyses, one showed a trace of albumin, and all showed red blood cells and hyalin and granular casts. Numerous hemoglobin determinations varied from 39 to 60 per cent and white blood cell counts from 10,000 to 18,000 per cubic millimeter. Differential counts showed from 1 to 28 per cent eosinophilia. No malarial organisms could be found. Bromsulphalein test for liver function and gastric analysis were normal. Blood non-protein nitrogen was 51 mg per cent, and the urea clearance test showed 26 per cent and 38 per cent of normal in the first two hour specimens. Total serum proteins were 7.2 per cent with an A/G ratio of 0.4. Blood bilirubin was normal, and the glucose tolerance test showed a fasting blood sugar of 92 mg per cent, two hour specimen, 182 mg per cent, three hours, 214 mg per cent, and four hours, 156 mg per cent. Repeated blood and stool cultures and agglutinations were normal. Chest roentgen-rays showed no abnormalities except an old left basilar pleuritis. Pyelograms, and roentgenograms of the legs, feet, gastrointestinal tract, and gall-bladder were normal. Electrocardiograms were essentially normal. Biopsies of the deltoid and gastrocnemius muscles were reported "Well marked atrophy. The largest arteriole in this specimen has an eccentric perivascular lymphocytic infiltration strongly suggestive of periarteritis nodosa."

"Very severe periarteritis involving the smaller vessels, some of which show localized necrosis of their wall. Patchy atrophy in the voluntary muscle. Angiomyositis, so-called. No evidence of trichinosis." (Dr C V Weller)

For the first four days of hospitalization the patient had a daily fever ranging from 101° to 104° , following which he was afebrile for five days, when again there was a daily fever to 101° for five days. At this time the patient was started on sulfanilamide for 10 days, during which he was entirely afebrile. When the sulfanilamide was discontinued there was again daily fever to 100° or 101° . The patient had a chronic upper respiratory infection with much hoarseness, and there was an inter-

mittent progressive deafness. He was given vitamin supplements, blood transfusions, ferrous sulfate, and symptomatic care. There was some improvement at the time of discharge on April 15. The pulse averaged 100 per minute.

The patient was readmitted to the hospital on May 16, 1938 in a somewhat improved condition. Some of the previous symptoms persisted, and he complained of weakness and stated that his feet were always cold. Physical examination was essentially the same as previously except that there was no edema. The blood pressure was 100 mm Hg systolic and 65 mm diastolic. Urea clearance test showed 45 per cent and 37 per cent of normal function in the first two hours, respectively, and blood non-protein nitrogen was 125 mg per cent. Urinalysis revealed 2+ albuminuria, and hemoglobin was 44 per cent. He had an afebrile and almost asymptomatic hospital stay, being discharged on May 26 with final diagnoses of periarteritis nodosa, uremia, chronic glomerulo-tubular nephritis, secondary anemia, and emaciation.

A letter was received from the patient's physician on March 29, 1939, inquiring about his case, and stating that he was then suffering from nephritis. A subsequent letter stated that he became comatose and died on December 17, 1939, with the death certificate reading "acute uremia, myocarditis, chronic nephritis with hypertension."

Case 11 G J A, first admitted on December 27, 1939, is to be reported by Foster⁴. The outstanding features of this case were soreness and tiredness of the leg muscles, diplopia, and blurring of vision. Periarteritis nodosa was suspected and several biopsies showed angiomiositis. Treatment was with sulfanilamide. The patient later had multiple cerebrovascular accidents. Necropsy substantiated the diagnosis of periarteritis nodosa. Positive Kahn reaction reports in this case were considered to be false positives by the dermatology department.

Case 12 A J F, a 49-year-old white male, was admitted on January 3, 1940, with a history of having contracted a severe "cold" on July 15, 1939, with rhinitis, malaise, and a cough productive of a small amount of sputum. This condition persisted for two months and was followed by ease of fatigue, mild palpitation, and dyspnea on slight exertion. Four weeks prior to admission, dull pain occurred in both calves and thighs which was made worse by exercise and relieved by rest. He had had fever as high as 102.5°, with night sweats, anorexia, morning headache, weight loss, soreness of arms, and low-back pain. Following exposure to cold, the patient noticed that both hands became blue and then white. A normal color followed immersion of the hands in warm water. He had noticed that for a few weeks his urine had been dark and stained his underwear. One tablet of sulfanilamide had been taken three times daily for two weeks prior to admission. For five or six years he had been troubled with occasional spells of diarrhea at which time he had two or three watery stools daily. There has been no change in this during the present illness. Otherwise, the past history was essentially normal.

Physical examination revealed a well developed, well nourished male, not appearing acutely ill but with a slightly icteric tint to the sclerae. The temperature was 99.6°, pulse, 84 per minute, respiration, 20 per minute, and blood pressure, 108 mm Hg systolic and 78 mm diastolic. The nasal mucosa was markedly injected. The heart and lungs were normal. The liver edge was palpable and slightly tender 3 cm below the right costal margin in the mid-clavicular line. The extremities appeared slightly atrophied with slight tenderness present in the muscles of the calves and thighs. At times there was a splotchy, light blue color of the hands and feet. Otherwise, the examination was essentially normal.

The Kahn reaction was negative. Urinalysis revealed a faint trace of albumin, rare red blood cells, and a few hyaline and finely granular casts. Hemoglobin was 76 per cent and 79 per cent on two occasions. White blood cell counts were normal, with 7 per cent and 3 per cent eosinophilia on two differential counts. The stool examination showed a positive guaiac reaction. Phagocytic index for brucellosis and

typhoid-dysentery-brucella agglutinations were negative. No amebae were found in the stools. The sedimentation index was 0.83 mm per minute (corrected). Blood bilirubin was 0.5 mg per cent (indirect). The bromsulphalein liver function test showed 100 per cent retention of the dye in 30 minutes. Trichina antigen skin tests in dilutions of 1:10,000, 1:500, and 1:100 were all positive in 24 hours. Biopsy of the left gastrocnemius muscle was reported "Some of the medium-sized arteries show a marked thickening of their wall with reduction in the lumen. There is a perivascular infiltration of inflammatory cells of various types including an occasional eosinophile. Periarteritis nodosa. No evidence of trichinosis" (Dr R. C. Wanstrom). Chest and spine roentgen-rays were normal.

The patient had a daily afternoon fever as high as 100 degrees. Pulse rate averaged 85 per minute. He had few complaints while at bed rest and was discharged on the ninth hospital day, essentially the same as at the time of admission. He was instructed to continue getting much rest.

The patient was seen in the out-patient department on April 9, 1940, with a letter from the outside physician stating that the "jaundice deepened for a period of about three weeks until on January 23 he had a quantitative van den Bergh test of 5.6 mg per cent. His liver edge at this time was palpable at the level of the umbilicus and moderately tender. By the middle of February his jaundice had entirely disappeared, the liver had receded markedly in size, and he felt much better in every way, complaining of no pain in his extremities even though he was up and about a short time each day." The patient, at the time of this examination, stated that he had improved and had gained eight pounds in weight since discharge. Slight dyspnea was still present and recently he had been troubled with soreness in the heels. The blood pressure at that time was 138 mm Hg systolic and 85 mm diastolic. The hands were warm and slightly cyanotic, and feet were cold but pink. The liver edge was 2 cm below the right costal margin. Blood bilirubin was 0.1 mg per cent (indirect), and the bromsulphalein test showed less than 10 per cent retention in 30 minutes. Urinalysis was normal except for an occasional red blood cell. Hemoglobin was 95 per cent and white blood count 10,100 with 8 per cent eosinophiles.

The patient returned for another examination July 29 stating that he had improved, having gained 15 pounds in body weight since discharge from the hospital. There continued to be very slight ease of fatigue and dyspnea on exertion and occasional pain in the heels, insteps, and calves of the legs after exertion or walking. This was relieved completely by rest. Otherwise, he was asymptomatic at the time. He stated that in April he had quite severe testicular pain lasting for three days, with no recurrence. Examination at this time showed no abnormalities except a slight splotchiness of the palms of the hands. The blood pressure was 124 mm Hg systolic and 80 mm diastolic, and the liver was not palpable. Urinalysis, complete blood count, urea clearance test, and electrocardiogram were all normal.

When last seen on November 4, 1940, the patient was in better condition than he had been in over a year or more, and his body weight was greater than it had ever been before. He had continued to obtain much rest as previously instructed. His only symptoms were occasional minor shooting pains in his arms, heels and soles of his feet. For two days, two weeks prior to being seen, he had had a mild tight sensation in his head, which was similar to that which he had experienced occasionally for several years prior to the onset of the present illness. At this time, the patient recalled that in November, 1939, he had had swelling of his testicles with slight soreness for about a week. Physical examination revealed a healthy looking man with slight nasal congestion. Blood pressure was 148 mm Hg systolic and 94 mm diastolic. For the first time the left testicle was noted to be atrophic. The second aortic valve sound was somewhat loud. Otherwise, examination was normal. Urinalysis and blood examinations, including a differential count, were normal at this time except for a

white blood count of 11,900. A biopsy taken near the site of the previous biopsy unfortunately failed to include a fair-sized artery. However, "some of the smaller arteries show a definite thickening of their walls but the inflammatory infiltrations previously seen are largely absent in this specimen" (Dr R C Wanstrom).

Case 13 L M C, admitted on March 12, 1940, is to be reported by Scurry.⁵ This patient had the chief complaints of palpitation, fatigue, dyspnea, and fainting of four months' duration. There was also a sensation of constriction or pressure in the chest and one of numbness in the arms when they were in the dependent position. The clinical diagnosis was rheumatic heart disease, but necropsy showed an unexpected pulmonary periarteritis nodosa.

Case 14 H B, who was admitted on November 4, 1940 and is to be reported by Hamff,⁶ had a history of pains in the extremities and headache, the former beginning in July, 1940. For a period of three months, nine years ago, he had experienced a similar but less severe attack of pain in his extremities which was relieved by the extraction of several teeth. Ten days prior to admission the patient had sudden loss of consciousness for half a day. There had also been weakness, weight loss, abdominal pain, and blurring of vision. Blood pressure was 218 mm Hg systolic and 128 mm diastolic on admission. Periarteritis nodosa was suspected, but a gastrocnemius biopsy was negative. The patient then had a splanchicectomy. Biopsy of a left intercostal artery at that time showed periarteritis nodosa.

ADDENDA

A J F, Case 12, was again seen in December, 1941, at which time he had returned to work. He had developed no new symptoms and was feeling well. His blood pressure was normal, 120 mm Hg systolic and 80 mm diastolic. Also in December, 1941, a letter was received from the wife of H B, Case 14, stating that he had returned to work, that his blood pressure was 'normal,' and that he was feeling the best he had felt in 20 years.

The duration of life from onset of illness in Case 12 has, therefore, increased to two and a half years, and the average duration of the cases herein reported has increased to 14 months. The prognosis, at least in a few cases, seems slightly better than predicted previously. Furthermore, results in Cases 12 and 14 seem to substantiate the possibility that some improperly diagnosed cases of periarteritis nodosa may have longer duration of life than present reports indicate.

REFERENCES

- 1 HARRIS, A W, LYNCH, G W, and O'HART, J P. Periarteritis nodosa, *Arch Int Med*, 1939, **LXIII**, 1163-1182.
- 2 HAUSER, I J. Periarteritis nodosa, *Jr Michigan Med Soc*, 1934, **XXXIII**, 440-444.
- 3 CURTIS, A C, and COFFEY, R M. Periarteritis nodosa, a brief review of the literature and a report of one case, *ANN INT MED*, 1934, **VII**, 1345-1358.
- 4 FOSTER, D B. To be reported.
- 5 SCURRY, M McL. To be reported.
- 6 HAMFF, L H. To be reported.
- 7 VON HALL, F. Patho-histologische und experimentelle Untersuchungen über Periarteritis nodosa, *Virchow's Arch f path Anat*, 1920, **CCXXVII**, 90.
- 8 HARRIS, W H, and FRIEDRICH, A W. Experimental production of periarteritis nodosa, *Jr Exper Med*, 1922, **XXVII**, 219-230.
- 9 OPHITS, W. Periarteritis acuta nodosa, *Arch Int Med*, 1923, **XXVII**, 870-898.
- 10 FRIEDBERG, C K, and GROSS, L. Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease, *Arch Int Med*, 1934, **LIV**, 170-198.
- 11 MIDDLETON, W S, and MCCARTER, J C. The diagnosis of periarteritis nodosa, *Am Jr Med Sci*, 1935, **CXC**, 291-308.
- 12 HEPPEL, M, and TUBER, M. Necrotizing arteritis and subacute glomerulonephritis in gonococcus endocarditis: toxic origin of periarteritis nodosa. *Arch Path*, 1933, **XX**, 35-50.

- 13 KRAHVITZ, L, ROSENTHAL, M, and LOUGHIN, E H Periarthritis nodosa (necrotizing panarteritis) in childhood with meningeal involvement, *Am Jr Med Sci*, 1935, cxc, 308-317
- 14 LUMMIS, F R Periarthritis nodosa, *ANN INT MED*, 1936, x, 105-116
- 15 VINING, C W A case of periarthritis nodosa with subcutaneous lesions and recovery, *Arch Dis Child*, 1938, xiii, 31-44
- 16 COHLN, M B, KLINE, B C, and YOUNG, A M The clinical diagnosis of periarthritis nodosa, *Jr Am Med Assoc*, 1936, cxii, 1555-1558
- 17 BERGER, S S, and WITZ, M A Periarthritis nodosa, case report, *Jr Allergy*, 1938, ix, 489-496
- 18 WELSH, D R Polyarteritis nodosa, *Am Jr Path*, 1939, xv, 79-88
- 19 Case Records of the Mass Gen Hosp, *New England Jr Med*, 1939, ccxv, 600-604
- 20 MOTLEY, L Periarthritis nodosa with report of case showing unusual features and apparent recovery, *Jr Am Med Assoc*, 1938, cvi, 898-902
- 21 BOYD, L J, and NUSSBAUM, C Some clinical aspects of periarthritis nodosa, *Med Clin North Am*, 1936, xv, 973-984
- 22 HAINING, R B, and KIMBALL, T S Polyarteritis nodosa, *Am Jr Path*, 1934, x, 349-360
- 23 ROTHSTEIN, J L, and WELT, S Periarthritis nodosa in infancy and childhood Report of two cases in the literature, *Am Jr Dis Child*, 1933, xlv, 1277-1308
- 24 MOSCHOWITZ, E The nosological status of periarthritis nodosa, *Jr Mt Sinai Hosp*, 1938, v, 337-339
- 25 GOLDSTEIN, I, and WELSER, D Bilateral atrophy of the optic nerve in periarthritis nodosa, *Arch Ophth*, 1937, lxxv, 767-773
- 26 SPIEGEL, R Clinical aspects of periarthritis nodosa, *Arch Int Med*, 1936, lvi, 993-1040
- 27 MACDONALD, J A, and MOSER, R H Periarthritis and arteritis of the temporal vessels a case report, *ANN INT MED*, 1937, x, 1721-1726
- 28 KERNOHAN, J W, and WOLTMAN, H W Periarthritis nodosa, a clinicopathologic study with special reference to the nervous system, *Arch Neurol and Psychiat*, 1938, xxxix, 655-686
- 29 JACOBSON, V C Periarthritis nodosa With report of two cases associated with clinical syphilis, *Med Papers, Christian Birthday Vol*, 1936, 820-835
- 30 KUSSMAUL, A, and MAIER, R Ueber eine bisher nicht beschriebene eigenthumliche Arterienkrankung (Periarthritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht, *Deutsch Arch f klin Med*, 1866, i, 484-518
- 31 ARKIN, A Clinical and pathological study of periarthritis nodosa, report of five cases, one histologically healed, *Am Jr Path*, 1930, vi, 401-426
- 32 KEEGAN, J J Primary vascular nephritis, or renal periarthritis nodosa, *Arch Int Med*, 1925, xxvi, 189-203
- 33 LEISHMAN, A W D The clinical diagnosis of polyarteritis nodosa with a report of four recent cases, *Lancet*, 1937, i, 803-808
- 34 WEVER, G K, and PERRY, I H Periarthritis nodosa, report of a case with fatal perirenal hemorrhage, *Jr Am Med Assoc*, 1935, civ, 1390-1395
- 35 POWELL, R E, and PRITCHARD, J E Periarthritis nodosa with the report of a case involving one kidney, *Brit Jr Urol*, 1932, iv, 317-327
- 36 EMERSON, R S, SCHROEDER, H A, and MAYNARD, E P Periarthritis nodosa Its clinical recognition with report of an illustrative case, *Brooklyn Hosp Jr*, 1939, i, 107-114
- 37 FITZ, R, PARKS, H, and BRANCH, C F Periarthritis nodosa, report of a case, *Arch Int Med*, 1939, lxi, 1133-1165
- 38 BERNSTEIN, A Periarthritis nodosa without peripheral nodules diagnosed antemortem, *Am Jr Med Sci*, 1935, cxc, 317-324
- 39 PASS, I J Infarction of the liver, *Am Jr Path*, 1935, xi, 503-525

- 40 MORGAN, D R, LIEBER, M M, and STEWART, H L Hepatic infarction in myelogenous leukemia and periarteritis nodosa, *Am Jr Med Sci*, 1936, cxcii, 540-546
- 41 DUNBAR, J C Periarteritis nodosa with associated thrombocytopenic purpura, *Bull School Med, Univ Maryland*, 1936, xx, 138-148
- 42 Case Records of the Massachusetts Gen Hosp, *New England Jr Med*, 1938, ccxviii, 838-843
- 43 BARNARD, W G, and BURBURY, W M Gangrene of the fingers and toes in a case of polyarteritis nodosa, *Jr Path and Bact*, 1934, xxxix, 285-290
- 44 CARLING, E R, and HICKS, J A B Periarteritis nodosa, accidentally recognized during life, *Lancet*, 1923, i, 1001-1003
- 45 SCHOTTSTAEDT, W E R Periarteritis nodosa with remission of symptoms, *California and West Med*, 1932, xxxvi, 186-188
- 46 MACAIGNE, M, and NICAUD, P Periarterite noueuse (maladie du Kussmaul) a forme chronique, *Bull et mém Soc méd d hôp de Paris*, 1930, liv, 665-674
- 47 STOUT, R B Personal communication

ANTICIPATION AND DIAGNOSIS OF NEURO-CIRCULATORY ASTHENIA¹

By JOHN T. KING, F A C P, *Baltimore, Maryland*

IN the midst of World War I, when American physicians were widely scattered, meetings of such representative groups as this were unknown. It is likely that many medical officers of the armed Services, absorbed in their various duties, heard little of a condition known to certain of their colleagues as the irritable heart of soldiers, or neuro-circulatory asthenia or, perhaps, the effort syndrome. Some were satisfied with the official terminology D A H (disordered action of the heart). Those who remained in civil posts had little interest in the matter, since the disorder, by and large, is not a peace-time problem. Various stresses and strains of military life form the basis of the typical case.

Credit for the original description of the irritable heart is usually given to DaCosta,² who observed the syndrome among soldiers in hospitals toward the end of the American Civil War (1864). It is clear, however, that a number of clinicians were familiar with the condition. It was discussed in meetings of the profession in Philadelphia, where many soldiers, exhausted by the strain of warfare, dysentery, typhoid and other hazards, were languishing in military hospitals. Hartshorne, speaking before the College of Physicians of Philadelphia, June 3, 1863, stated that Alfred Stillé had made the first report. In a Presidential address before the Philadelphia County Medical Society on February 11, 1863, Stillé,³⁰ referring to the peculiar palpitation of soldiers, spoke as follows: "Its ordinary association with a frequent pulse, or one rendered so by the erect posture, seems to prove it to be an effect of muscular debility of the heart alone, or of that organ along with the rest of the muscular system. It was not attended with any irregularity of the pulse nor, ordinarily, with any distinct murmur in the heart, not even with a soft, blowing murmur, nor was any such observed in the arteries as an ordinary symptom." Stillé considered the condition to be characteristic of army life, in contrast with civilian. Four months later, Hartshorne⁶ noted that soldiers with this condition suffered from dyspnea after even moderate exertion, whereas there were no characteristic physical signs, such as cardiac dilatation or hypertrophy, they seemed overcome by army duties. Several months of hospital care only *improved*, never cured, his patients. He considered them unfit for full duty, though suited to light duty of various kinds.

Stillé's address was followed by its publication in 1863. His report, incomplete though it is in some respects, clearly antedates that of DaCosta, whose book was not published until 1864. A review of this book can be found in the American Journal of the Medical Sciences for October, 1864. Hartshorne's address appeared in the same journal in the same year. It is

* Read at the Boston meeting of the American College of Physicians, April 22, 1941

not clear whether Hartshorne or DaCosta should be given second place in this race for priority, but Stillé was *facile princeps*

Nevertheless, DaCosta cleared up certain features. He added the description of pain in the lower precordium to Stillé's picture. As etiologic agents, he found fatiguing marches, fever and diarrhea.

When the Office of the Surgeon-General²¹ issued the Medical and Surgical History of the War of the Rebellion in 1879, the irritable heart of soldiers was all but forgotten. Among five huge volumes, I could find merely a statement to the effect that of 200 men with irritable heart, DaCosta had found that 61 were suffering from diarrhea or had recently recovered therefrom.

Each designation—neuro-circulatory asthenia,* effort syndrome, and the irritable heart of soldiers—has its advantages. Perhaps the first is the most descriptive of the perverted physiology of the condition. Effort syndrome indicates the precipitating cause and the cause of the disability. The writer prefers the irritable heart of soldiers because of its historic implications and its American origin, its military association, and the central fact of the syndrome which, after all, according to the men involved, concerns itself primarily with certain uncomfortable sensations which they refer to their hearts.

THE CONDITION IN CIVIL LIFE

Outside military life the syndrome is uncommon. The explanation is simple: the large majority of predisposing and direct causes do not exist in civil life. Physical strain of a person who is not qualified to bear it adequately is perhaps the most frequent precipitating factor. In civil life a man has control over his own efforts, and, if not built to be a professional wrestler, he takes employment as a clerk, florist, or perhaps window-dresser. In the Army, the clerk or window-dresser has little choice of action. However, to make the picture more real, let me cite the following cases from my practice.

Case 1 A white man, aged 34, a radio salesman, had been in previous good health until an attack of typhoid fever in March, 1940. Convalescence was protracted because of "cardiac symptoms," manifested by tachycardia, fatigue on slight exertion, and pain in the lower left chest outside the cardiac apex. For six months he had drawn disability insurance, but this was finally cancelled. In January, 1941, examination showed a healthy-looking man, with a normal cardiovascular apparatus in every respect save a tachycardia (rate 100). He was unable to do as much work as formerly because of the ready fatigue and disagreeable cardiac pounding.

Case 2 A white business man, aged 59, had for one year been conscious of rapid pulse, with rate 80-90. His feet were cold. There was no dyspnea. After eating he suffered a sense of gas about the left lower rib border with some heartburn, relieved by soda. The tachycardia and the gas seemed to be related. He had finally become prostrated by carrying two suitcases upstairs. He had no actual dyspnea or pain other than the "gas." His cardiovascular apparatus showed nothing whatever abnormal, except his pulse rate was between 96 and 100 per minute.

* This terminology is now used in the new Standard Classified Nomenclature of Disease.

Some time later I was consulted by this patient's clergyman who told me that the patient was very unstable and at certain intervals, roughly every two years, he passed through phases when he became disagreeable, felt that people were treating him badly or insulting him. These phases would pass off spontaneously, probably being recurring depressions.

Neither of these patients has had rheumatic fever, and there was no reason to suspect organic disease in either, save the possible effect of the typhoid fever in the first one. They were both instances of the irritable heart, and represent important etiologic factors: first, infection, and the lure of capitalizing on the condition in case 1, and second, the unstable or emotionally sensitive background of some patients as shown in case 2. In civil life these men were able to adapt their work to their handicap. In the Army they would doubtless both have become casualties.

THE PRESENT PROBLEM

In the year 1916 the British military heart hospital treated 558 cases of the effort syndrome.¹¹ In a similar period over 300 cases passed through U S General Hospital No 9 at Lakewood, N J. About four-fifths of the British cases were drawn from France, whereas a larger proportion of American patients had not seen actual combat.

Now that Selective Service is upon us, it is clearly our duty to be cognizant of this syndrome and to prevent, so far as possible, the acceptance of potential cases into the armed forces. In this effort the internist and the psychiatrist must work together. Some cases will occur despite our care. The scope of the casualties will depend further upon several contingencies—the rapidity with which the troops must be trained, the prevalence of such infections as influenza, pneumonia, and dysentery, the length of convalescence permitted from such infections, and whether the troops see actual combat.

PREDISPOSING FACTORS

It is very difficult to predict who will break under the effects of infections, but there is general agreement that certain types of recruits are predisposed, physically or mentally, to the syndrome. At Lakewood, with the help of Campbell,² certain categories were recognized. One group consists of the *constitutionally inferior*—such men may be physically defective but mentally competent, mentally defective but physically adequate, or defective in both departments. Another is the group of *chronic invalids*—such men have suffered from cardiac symptoms for years, despite the absence of demonstrable heart disease. The importance of this group was emphasized by Friedlander and Freyhof.⁴ Some such men have had rheumatic fever and may have an actual myocardial defect, but many give a history of pure cardiac neurosis. Such are the men who, for some obscure reason, develop cardiac symptoms under mental or physical strain, whereas others develop indigestion, headache, or some other disorder. There is also the group which was designated at

Lakewood as the *emotionally sensitive*. Some break down following harrowing experiences, such as burial, intense bombardment, and the sight of mangled comrades. For example, a man may drive himself to stand up under gunfire, but he can not control the trembling of his legs, the sweating, and the palpitation of his heart. The conflict between a natural desire to run from the scene of battle and the subconscious lure of life in a hospital behind the lines on one hand, and the man's desire to do his duty on the other, is a debilitating one.

SYMPTOMS

Once established, the picture is characteristic, regardless of etiology. The man is *lackadaisical* because of the discomfort encountered on moving about. He may complain of cold even in moderate temperature, and may "hug" the stove. He may be prostrated by walking the length of a room. *Fatigue* is real and measurable, and not imaginary (King).⁷ *Sweat* may roll from the axillae, especially on exertion or during examination. *Tremor* is common and may be disturbing to the subject. *Giddiness* is common. On exertion or during excitement the *pulse rises*, the *heart pounds*, and *breathlessness* is experienced. *Precordial pain* is common. Though it has been reported as occasionally being referred to the left arm, the writer has not noted this. The typical pain is not so oppressive or so inspiring of dread as is true angina, rather, one derives the impression that it is more in the nature of a "stitch in the side," and is typically located in the lower precordium in the region of the cardiac apex. The extremities may be flushed and even cyanotic, are frequently cold and clammy. *Dermatographia* has been noted in a certain group.¹⁴ The writer does not recall this last symptom as a common finding since the normal white *tâche* seen on stroking the skin with a blunt instrument was found in the Lakewood tests with considerable regularity.

SIGNS

The patient may be of vigorous appearance, since the unstable and the undeveloped personality is no respecter of physique. A general constitutional inferiority, with emphasis on lack of physical development, may be recognizable at a glance.

Outside the "typus" of the man and the evidences of breathlessness and fatigue and a certain overactivity of the circulatory apparatus, there is little to distinguish the man with irritable heart. The writer,⁸ during World War I, recorded the auscultatory findings in 500 men who were doing regular army duty. Every peculiarity encountered in the examination of the man with irritable heart could be matched by frequent findings of similar peculiarities among normal men. True, the "overactive" heart stirs up rather often a cardio-respiratory murmur in the adjacent lung. Systolic murmurs over the pulmonary conus, and at the apex in the recumbent posture, are common, but they are physiologic and are in no way characteristic of the irritable heart.

The pulse is labile, being rapid under exertion or excitement, but almost invariably it can be found below 90 per minute after rest. Lewis¹⁰ gives the average figure as 85.

Muscular strength is frequently below par. Smith¹⁶ noted defective strength in certain muscle groups, at times a general lack of strength. This was demonstrated at Lakewood by means of the spring balance, and records of progress in strength under graded exercise could be made.

It is a medical commonplace, verified frequently in World War I, that the man with a long thin chest is likely to lack endurance. In Civil War days, Hartshorne⁶ noted that the cardiac impulse of men with soldier's heart was "sudden, a little less in force than normal." In a most careful teleroentgenographic study in World War I, Smith^{17, 18} found that the hearts of 69 men with irritable heart could be differentiated, as regards size, into two groups—those with cardiac symptoms of long standing, and those who acquired symptoms during Army service. In the former group, the hearts were somewhat smaller than normal, whereas measurements in men who acquired symptoms in the Army were similar to those of normal "control" subjects.

Extending such observations, Starr et al.¹⁹ have shown that persons who have symptoms of neuro-circulatory asthenia in peace-time not only show small hearts, but also diminished average cardiac output, stroke volume, and total cardiac work per minute.

The observations of Smith and of Starr and his associates are, then, in agreement as regards the reduced size of the heart in the individual who is liable to irritable heart either in peace-time or in military service. However, there remains a group in whom the heart is of normal size who break from the effects of war, such are the cases that follow infections, or the effects of actual gunfire, horrifying experiences or other forms of exposure to combat conditions.

DIAGNOSIS

Recognition of irritable heart is based largely on the symptoms and signs noted above. The syndrome is more or less uniform, but the background of the patients is so varied that each case must be studied individually.

Differentiation of the types of *chronic invalidism*, *intelligence defect*, and *emotional sensitivity* can be made only through a most careful anamnesis. The *physically defective* type may be recognized on inspection, or through exercise tests. The *post-infection* type gives a characteristic history.

The resemblance between this condition and hyperthyroid states is merely superficial. After one-half hour's rest, the pulse in irritable heart usually finds a level below 90 per minute, whereas in hyperthyroid states it usually exceeds 90. The basal metabolic rate in irritable heart is not elevated, on the contrary, it is frequently below the average figure, especially in the asthenic individual. The epinephrine test may be expected to prove positive in 60 per cent of men with irritable heart.²⁴ The reaction is rather leisurely,

beginning after an average lag of 12 minutes, and reaching a peak in 32 minutes. This contrasts with the reactions found by Goetsch⁵ in hyperthyroid states, which occurred "early," and with the reactions encountered in women at the menopause by Myers and King¹³ in which the reaction reached its peak in an average of eight minutes.

Tuberculosis may present a superficial resemblance to the irritable heart, by careless examination either condition may be mistaken for the other. However, the writer⁹ has shown that the relation between the two disorders is no more than coincidental.

Finally, some form of exercise test, with observation of the pulse reaction and degree of breathlessness and fatigue induced is essential to the diagnosis. American observers¹⁴ with Lewis in World War I found the simple test proposed by Meakins and Gunson¹² to be satisfactory. This test consists of putting the subject through 75 paces at an ordinary brisk walk, followed by walking up 27 steps (18 feet). If the pulse rate fails to return to its previous level in two minutes after the test, the man's endurance is presumed to be impaired, and he will probably prove unfit for full duty. It was pointed out, however, that this rule deserves some latitude in application.

THE PERVERTED PHYSIOLOGY

The symptoms concerned with this syndrome can be produced by a variety of stimuli, mental and physical. The results are much the same whether the man has built up a conditioned reflex to the sound of gunfire, is sent to duty too soon after influenza, or is an asthenic or constitutionally inferior individual unfit for service. In a majority of instances the syndrome may be reproduced by the injection of epinephrine, whereas no reaction is observed in healthy subjects. Since epinephrine acts on the sympathetic nerve-endings, it may be deduced that the sympathetic system in many such men is exceptionally sensitive, or at least unstable. Further evidence of vasomotor asthenia is the inability of patients with this syndrome to maintain the white vasomotor tache, produced by stroking the skin with a blunt instrument, as long as do normal men.

In military life the probable cause of many cases is emotion, causing an outpouring of epinephrine into the blood stream, the sensitive sympathetic nervous system is stimulated, with the production of the symptoms previously noted. In other words, the man is sensitive to his own epinephrine. A similar sensitiveness or instability may be caused by certain infections, whereas in other cases it is probably congenital and inherent in a constitutional inferiority.

THE PROSPECT

The condition is not likely to reach serious proportions unless our Army enters combat conditions though unwise training and infectious diseases not thoroughly compensated for by adequate convalescence may precipitate cases

at any time. In an attempt to "harden" troops by forced marches and lack of proper food and rest, men who might develop into good soldiers by gradual physical training may be broken. It is also important to observe the effect of serious illness in individual cases, and, if indicated, arrange a course of gradual physical rehabilitation. In any case, however, the purpose of an Army is to be prepared for war, and toward that end the present Army must be recruited. I am informed by the Office of the Surgeon-General that "mild" neuro-circulatory asthenia is no bar to acceptance into the Army, if the condition goes beyond this degree the man is rejected altogether. I am inclined to agree with this rule in principle, though it would seem wise to be rather careful in its application. A man may show a somewhat labile blood pressure and pulse under the excitement of being examined, yet his history may show that he is an "All-American" athlete. Such a man recently volunteered and was rejected. On the other hand, a man with similar findings may have been a chronic invalid, unaccustomed to exercise because it disagreed with him. In my opinion the athlete should have been accepted, but we shall indulge in hope versus experience if we induct the chronic invalid. If the recruit is clearly of one of the types likely to develop the syndrome of irritable heart, he should be rejected (i.e., placed in Class 4 as ordered by the Surgeon-General) unless the demand for man-power becomes such as to require the establishment of "limited duty" classes in the Army. It should be kept constantly in mind that the recruit is more than a neuro-muscular-circulatory mechanism, he must be considered as a *person* by authorities who wish to estimate his aptitude for military service.

CONCLUSIONS

Recognition of a potential case of irritable heart is the joint responsibility of the psychiatrist and the internist. The former must ask the internist whether the recruit's history and symptoms are explainable on physiologic grounds, the internist should enquire whether they result from defects of intelligence, emotion, or environment.

The psychiatrist should be expected to recognize potential cases based on

- A Intelligence defects
- B Unstable reaction to authority (parental, clerical, etc.)
- C Chronic invalidism, especially referred to the cardiovascular system
- D Emotional instability, sense of inferiority resulting from sex maladjustment, fear of warfare, fear of shirking, etc.

The internist should eliminate men with symptoms based on the following backgrounds

- A Recent infections
- B General physical (constitutional) inferiority
- C Cases with demonstrably small hearts
- D Asthenic habitus (with "ventral" heart)

E Neuro-circulatory sensitiveness (history of abnormal reaction to coffee, tobacco, and alcohol may afford a clue)

Special Tests Some form of exercise test is essential That suggested by Meakins and Gunson (v s) seems as good as any.

In doubtful cases it would be very desirable to apply the epinephrine test A positive response to injection of 0.5 cc of 1:1000 solution consists of a rise of blood pressure of 10 mm or more, a rise in pulse rate of 10 or more beats per minute, with tremor, nervousness, palpitation of the heart, sweating, and so on Men with positive reactions were found unfit for duty by Wearn and Sturgis²⁴, such men should be rejected today A negative response does not eliminate the diagnosis, since, although 60 per cent of men with irritable heart gave a positive reaction, 40 per cent with similar symptoms failed to respond The positive epinephrine test is merely additional evidence that the subject is poor material for military service

BIBLIOGRAPHY

- 1 ADDIS, T, and KERR, W J The relative frequency in recruits with and without thyroid enlargement of certain signs and symptoms which occur in neuro-circulatory asthenia, *Arch Int Med*, 1919, xxvi, 316
- 2 CAMPBELL, C MACFIE The role of instinct, emotion and personality in disorders of the heart, *Jr Am Med Assoc*, 1918, lxxi, 1621
- 3 DACOSTA, J M Medical diagnosis, 1864, J B Lippincott, Philadelphia
- 4 FRIEDLANDER, A, and FREYHOF, W L Intensive study of 50 cases of neuro-circulatory asthenia, *Arch Int Med*, 1918, xxi, 603
- 5 GOETSCH, E Newer methods in the diagnosis of thyroid disorders, *New York State Med Jr*, 1918, xvii, 259
- 6 HARTSHORNE, HENRY On heart disease in the army, *Am Jr Med Sci*, 1864, xlviii, 89
- 7 KING, JOHN T, JR Fatigue in irritable heart and other conditions, *Arch Int Med*, 1919, xxi, 527
- 8 KING, JOHN T, JR Auscultatory phenomena of the heart in normal men and in soldiers with irritable heart, *Arch Int Med*, 1919, xxi, 89
- 9 KING, JOHN T, JR A study of the incidence of pulmonary tuberculosis in soldiers with irritable heart, *Arch Int Med*, 1919, xxi, 238
- 10 LEWIS, THOMAS National health insurance, Medical Research Committee, London, 1918
- 11 LEWIS, T, COTTON, T F, BARCROFT, J, MILROY, T R, DUFTON, D, and PARSONS, T R Breathlessness in soldiers suffering from irritable heart, *Brit Med Jr*, 1916, ii, 517
- 12 MEAKINS, J C, and GUNSON, E B The pulse rate after a simple test exercise in cases of "irritable heart," *Heart*, 1916-17, vi, 285
- 13 MYERS, WALTER K, and KING, JOHN T, JR Observations on the menopause III *Bull Johns Hopkins Hosp*, 1930 xlvii 23
- 14 OPPENHEIMER, R S, LEVINE, S A, MORISON, R A, ROTHSCHILD, M. A, ST LAWRENCE, W, and WILSON, F N Report on neuro-circulatory asthenia and its management, *Mil Surg*, April and June, 1918
- 15 PEABODY, F W, CLOUGH, H D, STURGIS, C C, and WEARN, J T Effects of the injection of epinephrin in soldiers with irritable heart, *Jr Am Med Assoc*, 1918, lxxi, 1912
- 16 SMITH, BENJAMIN The possibilities of physical development in cases of effort syndrome by means of graded exercises *Arch Int Med*, 1919, xxi, 321

- 17 SMITH, BERTVARD Teleroentgen measurements of the hearts of normal soldiers, Arch Int Med, 1920, xxi, 522
- 18 SMITH, BERTVARD Teleroentgen estimations of heart size in cases of effort syndrome, Arch Int Med, 1920, xxi, 532
- 19 STARR, ISAAC JR, DONAL, J S, MARGOLIS, A, SHAW, R, COLLINS, L H, and GAMBLER, C J Studies of the heart and circulation in disease, estimations of basal cardiac output, metabolism, heart size, and blood pressure in 235 subjects, Jr Clin Invest, 1934, viii, 561
- 20 STILL, ALFRED Address before the Philadelphia county medical society, delivered Feb 11, 1863, Am Jr Med Sci, (new ser), 1863, xli, 185
- 21 U S. Surgeon-General's Office Medical and surgical history of the war of the rebellion, Part II, Vol I, p 494 1879, Government Printing Office, Washington
- 22 TAYLOR, M K Remarks on heart disease (as observed in the military service from 1861 to 1865 inclusive), Trans Am Med Assoc, Phila, 1867, xviii, 139
- 23 TOMPKINS, E H, STURGIS, C C, and WEARN, J T Studies on epinephrin II Arch Int Med, 1919, xiv, 269
- 24 WEARN, J T, and STURGIS, C C Studies on epinephrin I Arch Int Med, 1919, xiv, 247

THE CLINICAL MANIFESTATIONS AND DIAGNOSIS OF CHRONIC BRUCELLOSIS

By ROBERT C MANCHESTER, M S , M D , *Alliance, Ohio*

IN a private practice which included a large group of patients with chronic complaints an appreciable number gave stories strongly suggestive of chronic brucellosis. Agglutination tests sent to the state laboratory were consistently negative. The problem, then, was the correct recognition of a disease which, in its chronic form, exhibits protean but ill-defined manifestations, and the correlation of these varied clinical aspects.

That brucellosis exists as a chronic, protracted disease, in addition to the acute self-limited form, has been recognized by Hardy,¹ Huddleson,² Evans,³ Calder,⁴ Cameron and Wells,⁵ and others.

Evans³ recognized the unreliability of the accepted laboratory procedures for its detection. In a group of 28 chronic cases diagnosed clinically, the organism was recovered from the blood in but seven cases, 46 per cent gave negative agglutinations, or titers of less than 1:40 dilution, and in 39.3 per cent the intradermal test with brucellergen was negative. However, in 14 cases who had recovered completely the skin test was positive in 92 per cent.

Gould and Huddleson⁶ regarded the intradermal test with brucellergen as a reliable indicator of brucella infection. They believed that if the test was negative, brucellosis could usually be ruled out. A positive test, however, does not indicate clinically active infection. Menefee and Poston⁷ obtained a 10 per cent incidence of positive tests in a group of healthy students none of whom gave a history of active brucellosis. Meyer⁸ and Kolmer⁹ found that previous vaccine injections did not induce positive intradermal reactions. A positive reaction, therefore, can be regarded as having the same significance as a positive tuberculin in tuberculosis.¹⁰ It indicates past or present brucella infection but bears no relationship to clinical activity.

The test may be done with brucellergen as developed by Huddleson,² or with a suspension of heat killed organisms. Keller¹¹ and Angle¹² found brucellergen and a heat killed vaccine of *B. suis* and *B. abortus*† equally effective, although the latter gave a higher incidence of local sloughs and systemic reactions.

The agglutination test may be positive, in dilutions of 1:40 or more, without any evidence of clinically active brucellosis.^{2,7} In the chronic cases it remains negative in a much higher percentage than in the acute form.⁷

Evans³ found the opsonocytophagic index the least reliable of the laboratory methods. Thus it is clear that no single laboratory procedure can be relied upon as an indicator of active chronic brucellosis. Recognition of

* Received for publication September 6, 1941.

† Prepared by Jensen-Selberg Laboratories Inc., Kansas City, Missouri.

chronic cases remains a clinical problem using the laboratory procedures available as aids rather than as determining factors

Although recognizing the limitations of the intradermal test, it was felt that a comparative analysis of the positive and negative reactors in a group of patients with chronic complaints should reveal significant data on the varied clinical aspects of chronic brucellosis. Furthermore, information of value in differential diagnosis should be obtained. Therefore, 100 ambulatory patients with chronic complaints were skin tested and thoroughly studied clinically.

Tests were all done intradermally with 0.4 cc heat killed antigen of *B. suis* and *B. abortus*,* the same antigen used by Keller¹¹ and Angle¹². They were read on the fourth day. A red indurated papule 5–10 mm in diameter was regarded as 1 plus, an area 10–15 mm in diameter as 2 plus, an area 15 mm or over as 3 plus, and a local slough as 4 plus. Sedimentation rates were done by the Westergren technique. Satisfactory blood cultures and opsonocytophagic techniques were not available. The cases with cholelithiasis or peptic ulcer were confirmed by roentgen-ray.

The patients were drawn from a town and rural group in Ohio. Approximately 50 per cent used raw milk regularly from their own or neighboring herds. All had been exposed to raw milk in the past and a few were in direct contact with pigs as well as cows.

A comparative study of the skin test positive and negative groups is presented in chart 1 with analysis of the major presenting signs and symptoms. The term recurrent "grippe" is retained because it was invariably used by the patients in relating their histories to describe recurrent attacks of prostration, fever and malaise, with or without associated upper respiratory infection or rheumatism.

Thirty-eight per cent had positive skin tests, whereas in 62 per cent the reaction was negative. Chronic low-grade fever, headache, recurrent "grippe," night sweats, colds, angina pectoris, dyspnea, joint and muscle pains were noted much more frequently in the skin test positive than in the skin test negative group. Palpitation, chronic exhaustion, easy fatigability, nervousness and gastrointestinal complaints occurred with equal frequency in both groups.

Table 1 shows the distribution and grouping of pertinent symptoms and signs among the patients of the skin test positive group.

"Grippe" Eleven patients, or 29 per cent, of the positive reactors gave a history of recurrent "grippe" in contrast to an incidence of 8 per cent in the negative group. Cases 29 and 34 had typical attacks of clinical influenza similar to those encountered in the negative reactors. The remainder, however, described a rather characteristic clinical syndrome. It began with insidious prodromata of increasing exhaustion and joint manifestations or the onset was abrupt. The acute phase was characterized by chilliness or chills, prostration, malaise, headache, backache, fever, anorexia, sweating,

* Prepared by Jensen Salsbery Laboratories Inc., Kansas City, Missouri

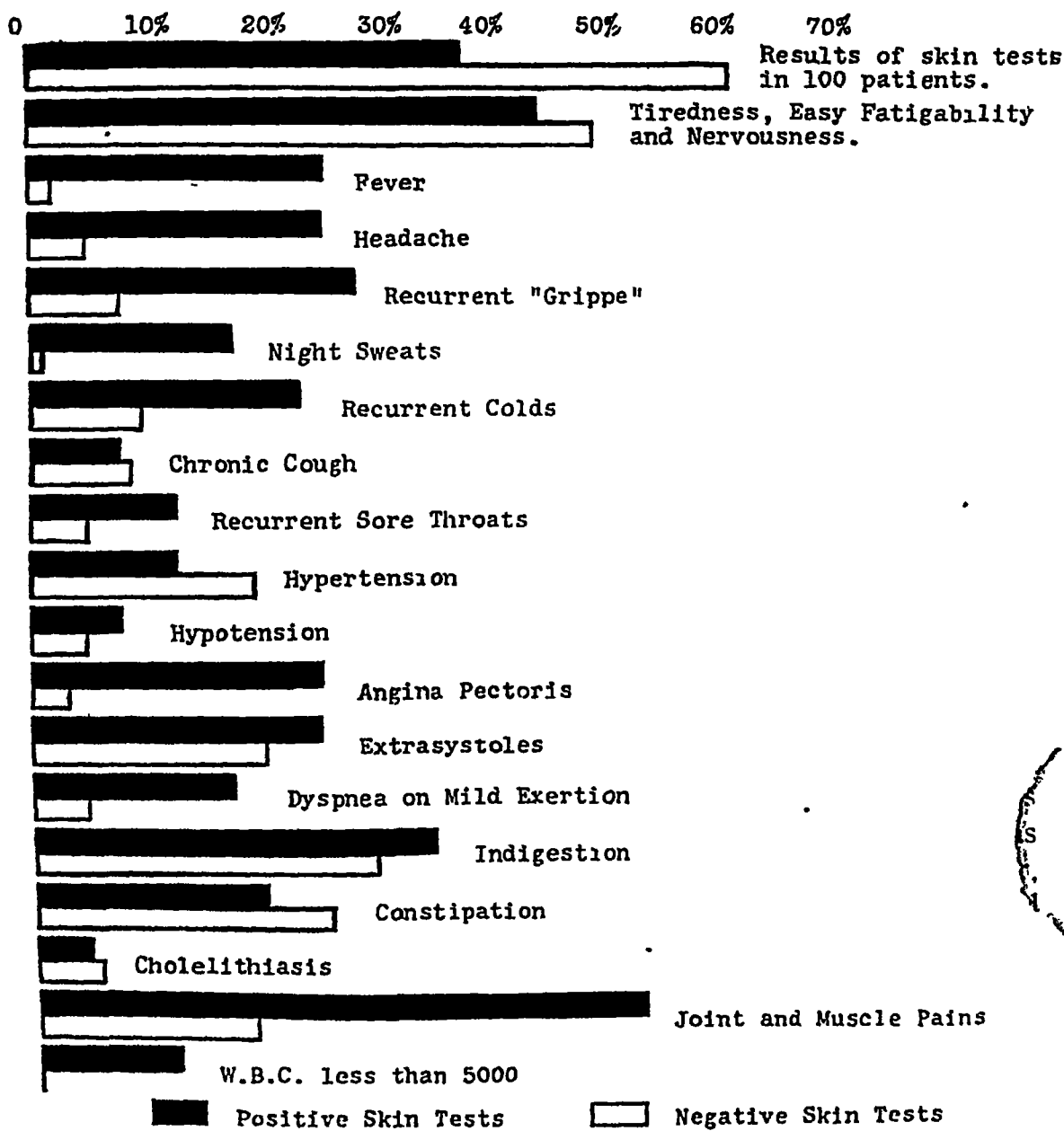


CHART I A comparative analysis of the major symptoms and signs observed in the skin test positive and negative groups

night sweats and sometimes gastrointestinal complaints, all merging into a prolonged period of convalescence. Joint manifestations and muscle soreness appeared in the prodromal period but more frequently in the acute or the convalescent phases. When present, upper respiratory complaints of rhinorrhea, cough or sore throat occurred most commonly several days after onset of the illness. Certain aspects suggest an attack of influenza. The long continued fever and other associated complaints, in the absence of focal complications such as sinusitis, are more compatible, however, with a recrudescence of brucellosis. Cough and upper respiratory manifestations are not unusual in chronic brucellosis.¹⁻⁵ Bogart,¹¹ Beatty,¹² and Lafferty and Phillips¹³ have described roentgenological changes in the lungs consisting of

increase in the hilar root shadows and peribronchial infiltration Carpenter¹⁶ has recovered the brucella organism from tonsillar tissue. Consequently, the associated upper respiratory manifestations are compatible with a recrudescence of brucellosis.

Coronary Disease The incidence of coronary artery disease is of particular interest as it has not been described previously as a feature of brucella infection. It occurred in 26 per cent of the skin test positive group in contrast to only 3.5 per cent in the negative reactors, although hypertension predominated in the latter group.

The associated pertinent symptoms have been listed in table 1. Additional information is summarized in table 2. The average age of onset for the group was 46.1 years with an average duration of symptoms of 6.5 years. In four, symptoms appeared in the third decade of life. None had valvular

TABLE I
The Distribution of the Pertinent Signs and Symptoms Found in the
Patients with Positive Intradermal Tests

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Sex	M	M	M	F	F	F	F	F	F	M	M	M	M	M	M	F	M	M	F
Age	40	38	32	45	28	53	34	37	63	20	52	33	58	55	24	45	21	72	42
Skin Test	xxxx	xx	xxx	xxxx	x	xxxx	xxxx	x	xx	xxx	xxxx	xxxx	xxxx	xxx	xxx	xx	xx	xxx	x
Chronic fatigue and nervousness	x			x	x	x		x		x	x		x			x			x
Temperature				x	x	x	x			x							x	x	
Headache	x			x	x	x	x	x		x					x				
current type				x	x	x		x		x								x	x
Night sweats	x			x	x	x	x			x								x	
Colds				x	x													x	x
Cough				x															
Sore throats																			x
Angina pectoris	x	x	x			x												x	
Coronary occlusion	x																	x	
Indigestion	x				x	x		x		x	x		x		x	x		x	x
Constipation	x				x					x			x		x	x		x	
Joint and muscle pains	x			x		x	x	x	x	x	x		x		x	x	x	x	x
Sedimentation rate mm. per hr	4	4	6	8	14	15		7	30	3	7		24			9	3		4
White blood count	7,300	9,800	4,700	6,800	4,600	7,900	10,700	9,100	6,000	10,500	6,300	5,700	9,100	4,300	5,900	5,500	4,500	5,900	8,300
Polys			50	69		60	69	63		54	62	53	58	65	42	49	66	63	72
Lymphs			39	26		32	26	29		41	26	34	30	27	47	39	27	37	23
Roentgen-ray of chest for TBC	neg			neg	neg	neg	neg			neg			neg				neg		
Systemic reaction to skin test				x		x	x						x						

TABLE I (Continued)

Case	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Sex	M	M	F	M	F	M	M	M	F	M	F	M	M	F	M	F	F	F	F
Age	25	30	46	45	50	67	64	33	64	14	46	47	67	54	11	14	7	20	44
Skin test	xxxx	x	xx	xx	xxxx	xxx	xxxx	xxxx	xxxx	xx	✓	xx	xxx	xxx	xxxx	xxxx	xx	x	xxxx
Chronic fatigue and nervousness	x		x	x	x		x				✓			x		✓			✓
Temperature			x													x			✓
Headache				x										x					
Recurrent "grippe"										✓		✓					x		x
Night sweats																			✓
Colds	x	x								x						x	x		x
Cough																	✓	✓	x
Sore throats		x								x						✓			x
Angina pectoris		x				x	x						x						x
Coronary occlusion													x						x
Indigestion	x		x	x									x	x					x
Constipation																			
Joint and muscle pains	x			x	x	x			✓		✓	x	✓			x			
Sedimentation rate mm per hr	3	9		7	5	13	10		11		10	6	7	7		10			6
White blood count	12,000	9,200	7,600	8,350	7,900	8,500	10,800	6,200	8,600		7,200	7,600	7,000	8,150	7,000	12,900	9,800		4,050
Polys	54	77	64	60	62	65		70	66		78			45	69	56	43		60
Lymphs	35	16	25	34	32	21		28	32		20			47	26	37	41		30
Roentgen-ray of chest for TBC			neg	neg							neg	neg				neg		?	neg
Systemic reaction to skin test								✓	✓										x

TABLE II
Coronary Artery Disease in the Group with Positive Intradermal Tests

Case	Sex	Skin Test	Age Onset Coronary Disease	Present Age	Duration in Yrs	Blood Pressure	Valvular Disease	Coronary Occlusion
1	Male	xxxx	32	46	8	140/78	No	Yes
2	Male	xx	37	38	1	120/70	No	
3	Male	xxx	31	34	1	135/85	No	
6	Female	xxxx	41	53	12	150/90	No	
18	Male	xxx	52	72	20	121/70	No	Yes
21	Male	✓	36	39	3	160/100	No	
25	Male	xxx	63	67	4	150/85	No	
26	Male	xxx	57	67	10	175/110	No	
32	Male	xxx	59	64	5	130/78	No	Yes
34	Female	xxxx	13	44	1	125/75	No	Yes

disease such as aortic stenosis, to account for the anginal symptoms. The two patients in the skin test negative group had onset of symptoms at the age of 58 and 61 years with blood pressures of 170 mm of Hg systolic and 90 diastolic and 180 mm systolic and 105 diastolic respectively.

A clinical diagnosis of chronic brucellosis was made in four of the positive reactors (cases 1, 6, 18 and 38)

The onset of angina in case 6, at the age of 41, followed an acute exacerbation of her chronic illness, which strongly suggests a causal relationship between the two. She had a temporal arteritis in one attack. This raises the question of a similar lesion in the coronary arteries as the underlying cause of her angina pectoris.

Horton and Magath¹⁷ have described temporal arteritis of unknown etiology with low-grade fever, malaise, headache and anemia in a group predominantly of farm women. One had involvement of the radial artery but none had coronary disease or joint manifestations. Agglutinations for brucellosis and cultures were negative. The clinical histories are not sufficiently suggestive to warrant a clinical diagnosis of brucellosis.

Eyre¹⁸ noted that the endothelium of the blood vessels was damaged so that blood easily passed through and localized extravasations of blood were frequently encountered in acute melitensis infections. However, no definite evidence of arteritis has been reported.

Case 38 developed symptoms of coronary disease at the age of 43 although her blood pressure had always been normal or low. The rarity of coronary disease in a woman of this age group without hypertension or other apparent cause makes the relationship to her brucellosis an interesting speculation.

Cases 1 and 18 both had long histories of chronic brucellosis. Case 1, a farmer all his life, had had symptoms between the ages of 14 and 18 years, recurring again around the age of 28 and continuing irregularly. Typical anginal attacks related to exertion and relieved by nitroglycerine and rest had recurred since the age of 32. When 43, he had had a severe attack of substernal pain, lasting "half the night," treated by his physician as coronary occlusion. Case 18 had anginal attacks which began at the age of 55. He had had recurrent symptoms of chronic brucellosis since the age of 25.

The age of onset of angina in cases 2, 3, and 21, at 37, 31 and 36 years respectively, is of interest. None of these patients had any other symptoms suggesting brucellosis.

Palpitation and extrasystoles were frequent complaints. No other cardiac manifestations were encountered with sufficient frequency to be considered significant.

Rheumatism Rheumatic manifestations were found in 55 per cent of the skin test positive group in contrast to 20 per cent in those with negative reactions.

The rheumatic complaints in the positive reactors are summarized in table 3. A large percentage showed widespread manifestations most frequently involving the small joints of the hands, the wrists, the lumbar region of the back, and the knees. A few complained primarily of arthralgias but the majority had definite stiffness along with the pain. Local swelling was fre-

TABLE III
The Distribution and Character of the Rheumatic Manifestations in the Group with Positive Intradermal Tests

Case	Sex	Age	Skin test	Sedimentation Rate mm per hr	Muscles	Hands	Wrists	Elbows	Shoulders	Back	Hips	Knees	Ankles	Feet	Manifestations
1	M	10	Slough xxxx	1	x	/	/			xxxx	xx	xx			Stiffness, aching, soreness, lumbago, sciatica
4	F	15	Slough xxxx	8	/	/	/			xxxx	xx	xx			Stiffness, aching, soreness, lumbago, swelling
6	F	53	Slough xxxx	15	xx	xxx	xx	/	/	xxx	xx	xx	xx	/	Stiffness, aching, soreness, swelling Recurrent swelling 3-4 week intervals
7	F	31	Slough xxxx	11								xxxx			Stiffness, aching, soreness Pain and soreness
8	F	37	/	7		/	/		/	xx	xx	xx			Stiffness, aching, soreness Pain and soreness
9	F	63	xx	30	/	/	/		/	xxxx	/	xx	xx		Stiffness, soreness, lumbago, sciatica
11	M	52	Slough xxxx	7	/	/	/	/	/	xxxx	xx	xx	xx		Stiffness, aching, soreness, lumbago
13	M	58	Slough xxxx	21	/	/	/	/	/	xxxx	xx	/			Sore tender muscles around shoulders
15	M	21	xxx		xx										Stiffness, aching, soreness Sore aching muscles—legs
16	F	15	xx	9	xx	/	/			xxx		xx	/		Soreness, aching, stiffness Stiffness, soreness, swelling, deformity
17	M	21	xx	3	xx	/	/	xx	/	xxx		/			Stiffness, aching
18	M	72	xxx	1	/	/	/	/	/	xxx		/			Stiffness, aching, soreness Localized tenderness, fibulo-tibial joint knee
19	F	12	/		xxx					xxx		/			Attack confined him to bed 6 months No residuals
20	M	25	Slough xxxx	3						xxx		/			Stiffness, aching, soreness
23	M	15	xx	75	/	/	/	/	/	/	/	/	/	/	Stiffness, aching, soreness Localized tenderness, fibulo-tibial joint knee
24	M	50	Gland xxxx	5	/	/	/	/	/	/	/	/	/	/	Attack confined him to bed 6 months No residuals
25	M	67	xxx	13	/	/	/		xx	xx		/			Stiffness, aching, soreness
28	F	61	Slough xxxx	11						xx					Soreness, swelling Aching, soreness, limited motion
31	F	17	xx	6					x	xxx	/	xx	/	x	Stiffness, soreness, in bed 3 attacks Migratory pain and stiffness
32	M	67	xxx	7		/	/	/	/	xxx	/	/	/	/	
33	F	51	xxx	7		/	/	/	/	xxx	/	/	/	/	
35	F	11	Slough xxxx	10	/	/	/	/	/	xxx	/	/	/	/	

quently noted but redness of the joint was not encountered. Eleven patients complained of muscle soreness.

Only one patient (case 19) showed joint deformities compatible with established rheumatoid arthritis. Her sedimentation rate was 4 mm per hour although the arthritic process was moderately active. None of the others, despite recurrent attacks or long continued manifestations, showed residual deformity or permanent loss of function.

Roentgen-rays in case 19 were compatible with rheumatoid arthritis. The others, with the exception of case 4, revealed nothing more than the hypertrophic changes compatible with their age. Case 4 showed extensive scattered areas of milium calcification in the left gluteal muscles which were considered to be due to myositis ossificans.

The striking laboratory feature of the group was the normal sedimentation rate in all except one (case 9), in spite of active joint manifestations, and, in some, of concomitant fever. In contrast, seven patients in the skin test negative group, who showed evidence of joint disease compatible with active rheumatoid arthritis, had sedimentation rates ranging from 24 to 68 mm per hour. Both groups complained of increased joint manifestations during the fall and winter months and after exposure to cold. In patients with other symptoms consistent with brucellosis the relationship of the joint manifestations to chronic brucella infection is quite definite. Those with joint symptoms as a more isolated complaint are more difficult to evaluate. The evidence would indicate, however, that chronic cases may exhibit little more than joint complaints of the character described.

Goldfain¹⁹ studied the incidence of brucellosis in a group of patients with rheumatic complaints, most of whom used raw milk. Thirty-one of 50 were diagnosed as having active brucellosis entirely on the basis of laboratory procedures. The rheumatic diagnoses in these 31 cases were atrophic arthritis in nine, or 29 per cent, hypertrophic arthritis in five, ankylosing spondylitis in one, and chronic fibrositis in seven.

The 29 per cent incidence of rheumatoid arthritis would indicate a relationship between rheumatoid arthritis and brucellosis which is not confirmed in the data presented. Therefore, 48 cases of characteristic, well developed rheumatoid arthritis were studied at the Peter Bent Brigham and the Massachusetts General Hospitals, Boston, Massachusetts. This group showed a 13 per cent incidence of positive skin reactions. Furthermore, 175 other patients entering the Peter Bent Brigham Hospital were skin tested to determine the expected incidence of positive reactions. Eleven per cent gave positive tests. The close agreement between the two groups indicates that brucella infection does not play any significant etiologic rôle in rheumatoid arthritis. Sedimentation rates were elevated above normal in all the cases of rheumatoid arthritis tested.

These results are in agreement with Green and Freyberg²⁰ who found no evidence of brucellosis in 25 cases of typical rheumatoid arthritis. Of 25 patients with joint symptoms and manifestations not compatible "with any

of the common arthritides," three had "quite convincing evidence of active brucellosis" and six others had possible brucellosis

Invariably, both *headache*, and *chronic fatigue* and nervousness were accentuated during the "grippe"-like attacks and the subsequent convalescence in the positive reactors. Except for this, there were no differences in the character of these complaints in the positive and negative groups. The incidence of migraine was almost identical in both groups. Cases 1, 4 and 7 (positive reactors) had migraine. Attacks were more frequent in periods of ill health but no other relationship was noted.

Gastrointestinal complaints were similar in both groups. Three patients in the skin test positive group had peptic ulcer. It is of interest that two of them had used raw milk and cream on prolonged Sippy régimes while the only patient with peptic ulcer in the skin test negative group had used little raw milk. Harris²¹ has commented on the occurrence of peptic ulcer in brucellosis patients. Heavy exposure to raw milk and cream on Sippy régimes may be the responsible factor.

"*Protracted fevers*" ranged from 99.2° F to a little over 100° F. The fever reached its peak in the afternoon and was usually normal or only slightly elevated in the morning. Physical and mental strain was apt to result in higher afternoon temperatures.

The *white count* showed some tendency to leukopenia in the positive skin test group. Five had white counts below 5000, whereas none of the negative reactors was below that level. Otherwise, the range was the same in both groups. Two of the 13 cases diagnosed clinically as chronic brucellosis had white counts below 5000. The remainder varied from normal to a moderate leukocytosis.

Table 1 shows the *skin test reaction* in relation to the patients' symptoms. There is no consistent correlation between the two. Local sloughs were encountered in 42 per cent. An appreciable number had associated lymphangitis and axillary adenitis lasting a few days. Local ulcers healed in the course of seven to 21 days. Systemic reactions with fever from 100° F to 102° F, malaise, prostration and headache were encountered in seven cases. In cases 28 and 38 a moderate systemic reaction lasted from 10 to 14 days. Case 38 had a moderate accentuation of her angina pectoris indicating that caution should be used in skin testing such cases. Cases 12 and 27 had local sloughs and systemic reactions, although neither ever had any symptoms compatible with brucellosis. Dustin²² has considered a febrile response to antigen as one of several tests of clinical activity. Such an assumption is unjustified and the skin test reaction can not be considered as an index of clinical activity. One patient in the negative group presented a clinical picture compatible with chronic brucellosis. With this exception, the intradermal test was an accurate indicator of brucella infection.

The data presented indicate that the more common manifestations in chronic brucellosis are chronic fatigue and nervousness, protracted low-grade fever, recurrent "grippe"-like attacks characteristically with prolonged con-

valescence, night sweats, palpitation, gastrointestinal symptoms and joint and muscle complaints. Coronary artery disease may be a part of the clinical picture.

The clinical combinations which were encountered most frequently are presented by reviewing representative case histories.

CASE REPORTS

Case 6 This female aged 53 years, had spent her life on a farm, had milked the cows when able and had regularly used raw milk from a herd found to be heavily infected. She complained of rheumatism, exhaustion, nervousness and substernal pain on exertion.

Her ill health began at the age of 16 with an attack of rheumatism, which confined her to bed for about three months. "More or less rheumatism" had persisted since then, worse in the winter and on damp days. Joint manifestations consisted of pain and stiffness, most frequently involving the small joints of the hands, wrists, elbows, shoulders, back, knees and ankles. Moderate swelling occurred but never any redness or permanent loss of function. Muscle soreness often accompanied the rheumatism. The pectoral muscles were prone to soreness after hard work and the patient suffered from recurrent "lumbago."

"Grippe" had recurred irregularly since childhood, as often as several times a year in summer or winter, particularly if she overworked. The onset was insidious with increasing joint manifestations and exhaustion, or, at other times, more abrupt. The acute phase was characterized by chilliness or chills, generalized aching and soreness, prostration, fever, night sweats, headache, backache, increased joint stiffness, and often moderate swelling particularly of knees or ankles. Rhinorrhea, cough and sore throat often appeared on the second to fourth day of the attack. The acute phase gradually improved in from 7 to 10 days, merging into a prolonged convalescence which lasted from two or three weeks up to several months. This consisted of low-grade fever, exhaustion, night sweats, headaches and joint manifestations, all of which gradually improved. A severe attack at the age of 41 confined her to bed for 12 weeks. Her physician, at that time, stated that her heart was affected and limited activity was prescribed for another three months. Since then she had complained of dyspnea and of a tight clutching feeling in the substernal area precipitated by exertion and relieved by rest.

Long standing symptoms of nervousness, tiredness and easy fatigability became worse as she grew older. Epigastric gas and fullness after meals appeared. The bowels were always regular.

For several months before she was first seen exhaustion, nervousness and rheumatism had grown worse, epigastric gas and fullness had increased, appetite had become poor, and she was unable to do her own housework.

Physical Examination Temperature 99.4° F, pulse 82, blood pressure 150 mm of Hg systolic and 90 mm diastolic. She was rather obese and was well preserved in spite of the long history of ill health. The knees, ankles, right elbow, wrists and small joints of the hands were painful and stiff on motion. Both knees were puffy. The distal joints of the fingers showed small Heberden's nodes. No A-V nicking was noted in the ocular fundi. The teeth and tonsils had been removed. Thyroid was small. No general adenopathy was noted. The lungs were clear. The heart was somewhat enlarged, sounds were regular and of good quality, no murmurs were heard. Abdominal examination was negative. The spleen was not palpable. Pelvic and rectal examinations were negative.

Laboratory Findings Hemoglobin 98 per cent, red blood cells 5,190,000, white blood cells 7900, polymorphonuclears 68 per cent, lymphocytes 32 per cent, mononuclears

4 per cent, eosinophiles 2 per cent. Urine revealed a trace of albumin. Kahn and Klhne tests were negative. The electrocardiogram was within normal limits. There was no axis deviation. A six-foot film showed a transverse cardiac diameter of 15.5 cm, with chest measurement of 29.5 cm. Sedimentation rate was 15 mm in one hour. Brucella agglutination was reported negative by the state laboratory. Cholecystograms and sinus roentgen-rays done later were negative. Roentgenograms of knees showed hypertrophic changes compatible with age.

Course. After 10 days of increasing symptoms the patient had abrupt onset of chills with temperature to 103° F. Severe generalized aching and soreness, backache, nausea and vomiting developed. A reddened, indurated, erysipelas-like area appeared over the nose and cheeks in butterfly distribution. Both knee joints showed evidence of free fluid. Large doses of sulfanilamide resulted in no improvement except that the facial lesion did not spread. Agglutinations were again negative. The white count was 5000. Her condition improved in the course of two weeks and the facial lesion cleared up. At this time an intradermal test with brucella antigen was done. Twelve hours later, the original severe clinical picture reappeared including the erysipelas-like lesion over the face. A large local reaction developed at the skin test site with redness, swelling, lymphangitis and axillary adenitis. The local area sloughed, requiring three to four weeks to heal. The recrudescence of her illness subsided in three or four days, but convalescence was slow. She complained of soreness over the scalp and an area of thickening and tenderness was noted along the course of the right temporal artery.

Brucella vaccine alone intramuscularly was ineffective. However, a course of sulfanilamide and vaccine together caused striking improvement. The butterfly erysipeloid reaction on the face, recurring twice in association with the systemic reaction to vaccine, showed that it was a specific reaction.

Rheumatism again reappeared, after four months of good health. Agglutinations were negative. Sedimentation rate was 12 mm per hour. Vaccine and sulfanilamide again resulted in striking relief of symptoms. Anginal attacks were controlled with nitroglycerine. Her blood pressure averaged 150 systolic and 90 diastolic.

Comment. A diagnosis was made of *chronic brucellosis* with recurrent acute attacks, mild hypertension and coronary heart disease with angina pectoris. The acute attack described was of particular interest because of the erysipeloid facial eruption reproduced by vaccine, and the temporal arteritis. No other cases of temporal arteritis were encountered in this series. Skin manifestations have been described in acute attacks by Simpson¹ and others. The long duration of symptoms is noteworthy. The agglutination test remained negative even after vaccine therapy.

Case 10. This male, aged 25 years, had his first contact with raw milk on a vacation at the age of 23 years. At that time, he developed "grippiness" with aching, weakness, fever, night sweats, diarrhea and upset stomach which lasted two or three weeks. Since then similar attacks had recurred. A stuffy cold and mild sore throat often appeared during the attack. He had observed a tendency to afternoon temperatures from 99° F. to 100° F. and diminished stamina. A hard day's work increased his fever and often precipitated headache, exhaustion and muscular aching. His attacks seemed to be caused by periods of overwork and gradually cleared up on a better rest. He had never had any hemoptysis or chronic cough and there was no history of exposure to tuberculosis.

Physical Examination. Temperature 99° F., pulse 85, blood pressure 110 systolic and 70 diastolic. He was well developed and nourished, and did not appear ill. Gen-

eral examination revealed nothing whatsoever. No foci of infection could be found. The tonsils had been removed. The lungs were clear. The heart was negative. The spleen was not palpable, and there was no general lymphadenopathy.

Laboratory Findings Red blood cells 5,310,000, white blood cells 6000, hemoglobin 103 per cent, polymorphonuclears 54 per cent, lymphocytes 41 per cent, mononuclears 5 per cent. Urine was negative. Kahn and Kline tests, and agglutinations for brucella were reported negative by the state laboratory. Sedimentation rate was 3 mm per hour. Roentgenograms of chest, sinuses and teeth were negative. Prostatic smear showed nothing. Skin test with brucella antigen was 3 plus.

Course He was placed on high vitamin régime with rest periods and avoidance of raw milk. In four months his condition improved.

Comment This patient was considered to have low-grade brucella infection with mild recrudescences. The relation of the subacute attacks and chronic symptoms to physical and mental strain observed in this case was also noted in others.

Case 35 This female, aged 15 years, had spent her entire life on a farm and had always drunk large quantities of raw milk. The herd was heavily infected. For six or seven years she had had migratory aching, stiffness and soreness in her knees, ankles, elbows, shoulders, wrists, hands and back. She suffered from frequent colds but gave no history of "grippe." She had occasional night sweats, tired easily and was nervous at school.

Physical Examination Temperature 100° F, pulse 81, blood pressure 110 systolic and 90 diastolic. She was well developed and nourished and did not appear ill. No objective evidence was found of joint disease although she complained of subjective pain in the wrists, knees, left elbow and hands. The sinuses were clear. Her teeth were in good repair. The tonsils had been removed. The heart and lungs were negative. The spleen was not palpable, and there was no glandular adenopathy.

Laboratory Findings Red blood cells 4,670,000, white blood cells 12,900, hemoglobin 84 per cent, polymorphonuclears 50 per cent, stabs 6 per cent, lymphocytes 38 per cent, mononuclears 6 per cent. Urine was negative. The state laboratory reported Kahn and Kline tests and agglutinations for brucellosis negative. Roentgenograms of her chest, sinuses, and knees were within normal limits. Electrocardiogram was negative. Sedimentation rates on repeated examinations ranged from 8 to 12 mm per hour. Skin test for brucellosis was strongly positive accompanied by a local slough. Her temperature, checked repeatedly, always ranged between 99° and 100.3° F in the afternoons.

Comment Chronic brucellosis of the type described in this case was encountered usually in the younger age groups. Little fluctuation was observed in the severity of the symptoms. The rather marked joint symptoms and myalgias with no objective findings in the joints were a striking feature. The normal sedimentation rate and absence of heart disease or electrocardiographic changes were useful in differentiating this form from rheumatic fever.

Case 38 This female, aged 44 years, had used raw milk until approximately 32 years of age. Since then exposure had been irregular, chiefly limited to several vacations in the country each year.

She had been a tuberculosis suspect for 25 years because of persistent afternoon temperature, exhaustion and night sweats. Hospitalization several times in sanatoria

had revealed no evidence of tuberculosis and a diagnosis had never been established. She had been subject to frequent colds and "grippe" for many years. This "grippe" was characterized by chilliness and less often by chills, fever, severe prostration, malaise and drenching sweats, and increase in her afternoon temperature. Colds and cough sometimes appeared at the beginning but more often during the course of the "grippe." For two years dyspnea on exertion and afternoon swelling of ankles had been noted. In January 1939, she had an abrupt onset of a tight aching substernal distress radiating into the neck, accompanied by a choking sensation which lasted three or four hours. Since then, similar attacks of short duration had occurred on exertion and were relieved by rest. Symptoms typical of peptic ulcer had recurred irregularly and once she had vomited blood. These symptoms were relieved by powders and Sippy regimes. For five years her periods had been excessive. There was no history of rheumatism or headache. The white count and blood pressure had always been reported "below normal."

Physical Examination Temperature 99° F, pulse 78, blood pressure 120 systolic and 70 diastolic. She was well developed and nourished and appeared in good health except for rather pale mucous membranes. The head, eyes, ears, nose and mouth disclosed nothing abnormal. The vessels of the ocular fundi were normal. The lungs were clear. No cardiac enlargement was found. The sounds were of fairly good quality and no murmurs were heard. The liver and spleen were not enlarged. Several small fibroids were found on pelvic examination. Minimal pretibial edema was present.

Laboratory Findings Red blood cells 4,160,000, white blood cells 4050, hemoglobin 70 per cent, polymorphonuclears 53 per cent, lymphocytes 37 per cent, mononuclears 9 per cent, eosinophiles 1 per cent. Urine was negative. Sedimentation rate was 6 mm in one hour. The state laboratory reported Kahn and Kline tests and agglutinations for brucellosis negative. Roentgenograms of her chest showed nothing abnormal. No evidence was found of old or recent tuberculosis. The cardiac silhouette was within normal limits. A gastrointestinal series revealed some deformity of the cap but no evidence of active ulcer. Cholecystograms were negative. The electrocardiogram showed a QRS time of 0.12 second with a prominent S-wave in Lead I interpreted as intraventricular block. Skin test with brucella antigen was 4 plus. A lymphangitis, axillary adenitis and systemic reaction developed. She had severe drenching sweats, fever and a noticeable increase in her anginal symptoms for several weeks after the skin test.

Comment This patient was considered to have chronic brucellosis, coronary artery disease with angina pectoris, and uterine fibroids with secondary anemia. No joint manifestations ever appeared in spite of the long history of infection and subacute recrudescence.

Case 23 This male, aged 45 years, kept his own goats and cows. Three years previously his son had had an acute febrile illness which was diagnosed as brucellosis by positive agglutination tests.

At the age of 41 the patient had had an illness which began with migratory joint and muscle pains but, in the course of a month, developed into a clinical picture of severe generalized aching and soreness, mental depression, nervousness, physical exhaustion, sweating, headache, vertigo, anorexia, indigestion and weight loss. After three weeks he had recovered sufficiently to return to part time work.

Since that time he had never regained his health but had continued to have varying degrees of migratory joint and muscle pains, headaches, recurrent dizziness, light-headedness, indigestion and exhaustion worse in the afternoon. His joints had been free of swelling and his past health had always been excellent.

Physical Examination Temperature 98.3° F., pulse 85, blood pressure 130 systolic and 70 diastolic. He was a thin but well preserved man. Tenderness was noted over the sterno-manubrial junction and the right trapezius. Otherwise, the joints and muscles were entirely normal. His eyes, ears, nose and mouth disclosed nothing abnormal. The tonsils had been removed. The thyroid was small. Nothing was found in the heart or lungs. The liver and spleen were not enlarged. The prostate was normal. Reflexes were all active and equal.

Laboratory Findings Red blood cells 4,450,000, white blood cells 8350, hemoglobin 60 per cent, polymorphonuclears 60 per cent, lymphocytes 34 per cent, mononuclears 6 per cent. Urine was negative. Serologic tests for syphilis and agglutinations for brucellosis were reported negative by the state laboratory. Intradermal test for trichinae, negative. Brucellosis skin test, 2 plus. Sedimentation rate, 7 mm in one hour. Roentgenograms of chest, teeth, hand, wrist and sinuses, negative. Uric acid, 3.2 mg per cent. Basal metabolic rate, 2 plus.

Course He was observed over a period of eight months. On a rest and high vitamin regime with removal of sources of exposure and two courses of brucella vaccine he obtained approximately 60 per cent improvement.

Comment This patient represents a type of case in which accurate diagnosis is difficult. However, in view of his son's acute attack during the patient's own illness, a clinical diagnosis of chronic brucellosis seems warranted. His temperature was consistently normal.

SUMMARY

Brucellosis should be recognized as a chronic systemic infection capable of persisting through many years of a patient's life. Constant reinfection may have been a factor in this series since exposure had continued unchecked in most cases.

The clinical manifestations are variable. Nevertheless, various combinations of protracted fever, chronic fatigue and nervousness, recurrent "grippe"-like attacks characteristically with prolonged convalescence, headache, palpitation, gastrointestinal complaints, joint pains and myalgias should suggest chronic brucellosis. Cases representative of the clinical combinations most frequently encountered by the author have been presented.

It is suggested that coronary artery disease may be caused by chronic brucella infection. The temporal arteritis which occurred in case 6 indicates that the underlying pathology may be an arteritis of the coronary arteries. These observations require confirmation by the study of additional patients in areas where brucellosis is endemic.

Joint manifestations consisted of arthralgias, pain and stiffness in the involved joints and frequently moderate swelling. No redness was observed. A characteristic feature was the absence of residual deformity or permanent impairment of function. No relationship was found between brucellosis and rheumatoid arthritis. A normal sedimentation rate is of value in differentiating active phases of rheumatoid arthritis from brucellosis.

In this series the intradermal test was a reliable index of brucella infection. Only one case with a negative skin test presented a clinical picture

compatible with brucellosis. It is to be emphasized that neither the skin test nor the severity of the local or general reaction gives any reliable information as to whether the infection is active or latent.

BIBLIOGRAPHY

- 1 HARDY, A. V. Undulant fever with special reference to a study of brucella infection in Iowa, Nat Inst of Health, Bull 158
- 2 HUDDLESON, I. FOREST, ET AL. Brucellosis in man and animals, 1939, The Commonwealth Fund, N. Y.
- 3 EVANS, ALICE C. Studies in chronic brucellosis. I. Introduction. Pub Health Rep, 1937, lli, 1072-1077.
EVANS, ALICE C., ROBINSON, FRANK H., and BAUMGARTNER, LEOA. Studies on chronic brucellosis. IV. An evaluation of the diagnostic laboratory tests, Pub Health Rep, 1938, liii, 1507-1523.
ROBINSON, FRANK H., and EVANS, ALICE C. Chronic brucellosis in Charlotte, N. C., Jr Am Med Assoc, 1939, cxiii, 201-206.
EVANS, ALICE C. Difficulties in the diagnosis of chronic brucellosis, Am Jr Trop Dis, 1939, xix, 319-325.
- 4 CALDER, ROYAL M. Chronic brucellosis, South Med Jr, 1939, xxii, 451-458.
- 5 CAMERON, W. ROSS, and WELLS, MARIAN. Undulant fever control in Washington County, Md, South Med Jr, 1934, xxvii, 907-912.
- 6 GOULD, S. E., and HUDDLESON, I. F. Diagnostic methods in undulant fever (Brucellosis), Jr Am Med Assoc, 1937, cxv, 1971-1974.
- 7 MENEFEE, E. E., and POSTON, MARY A. Significance of standard laboratory procedures in the diagnosis of brucellosis, Am Jr Med Sci, 1939, xcvi, 647-653.
- 8 MYER, K. F., and EDDIE, B. Laboratory infections due to brucella infection, Jr Infect Dis, 1941, lxviii, 24-32.
- 9 KOEHLER, JOHN A., BONDI, AMEDEO, JR., and RUIF, ANNA M. The results of active immunization of human beings with a mixed heat killed vaccine of *B. typhosus*, *B. abortus* and *B. melitensis*, Jr Infect Dis, 1940, lxvii, 258-267.
- 10 MCGINTY, A. PARK, and GAMBRILL, W. ELIZABETH. Chronic brucellosis, The New Internat Clin, Vol I, New Series, Two, March 1939, p. 1.
- 11 KRIEGER, ALVIN E. Comparison of skin tests obtained with brucellergen and heat killed brucella organisms in sensitized individuals, South Med Jr, 1940, xxiii, 1180-1182.
- 12 ANGEL, FRED E., ALLEN, WM. H., BAUMGARTNER, LEOA, and LUNSFORD, W. F. Skin testing for brucellosis (undulant fever) in school children, ANN INT MED, 1938, xii, 495-501.
- 13 BOWAIT, F. B. Pulmonary changes in undulant fever, South Med Jr, 1936, xxix, 1-9.
- 14 BEATTY, OPEN A. Manifestations of undulant fever in the respiratory tract, Am Rev Tuberc, 1937, xxxvi, 283-289.
- 15 LAFERTY, ROBERT H., and PHILLIPS CLAUDE C. Pulmonary changes in patients suffering from Malta fever, South Med Jr, 1937, xxx, 595-600.
- 16 CAMPBELL, CHARLES M., and BOAK, RUTH A. The isolation of *Brucella abortus* from humans, Jr Am Med Assoc, 1932, xcix, 296-298.
- 17 HESTON, B. T., and MAGATH, T. B. Arteritis of the temporal vessels, report of 7 cases. Proc Staff Meet Mayo Clin, 1937, xii, 548-557.
- 18 LADD, J. W. H. Melitensis septembris. Lancet, 1908, i, 1747-1752.
- 19 GILBERT, F. Chronic arthritis and undulant fever: their interrelationship, Jr Oklahoma Med Assoc, 1938, xxxi, 111.
- 20 LADD, J. W. H. Septic arthritis cases with associated undulant fever findings, South Med Jr, 1938, xxxi, 325-327.

- 20 GREEN, M E, and FRIEDBERG, R H The incidence of brucellosis in patients with rheumatic disease, *Am Jr Med Sci*, 1941, cci, 495-504
- 21 HARRIS, HAROLD J Undulant fever (brucellosis), difficulties in diagnosis and treatment, *New York State Jr Med*, 1937, xxxvii, 1295-1301
- 22 DUSTIN, CECIL C, and WYLLIE, HENRY L C Chronic brucellosis I The incidence of chronic brucellosis in Rhode Island, *New England Jr Med*, 1940, ccxvii, 670-673
- 23 SIMPSON, WALTER M Undulant fever (brucellosis), a clinico-pathologic study of ninety cases occurring in and around Dayton, Ohio, *ANN INT MED*, 1930, iv, 238-258

FAMILIAL SYRINGOMYELIA AND STATUS DYSRAPHICUS

By BERT E. MULVEY, M D , F A C P , and LEA A. RIELY, M D , F A C P ,
Oklahoma City, Oklahoma

DURING the last three years, we of the peripheral vascular department of the University Hospital have had the privilege of studying several members of a very interesting family. Various individuals of this group present signs and symptoms of impaired circulation to the extremities, disturbance of sensation in the lower limbs and feet, and a few members, similar disturbances in the hands. Slow-healing ulcers were present in the feet of some. Structural anomalies and the so-called stigmata of degeneration were present to an astonishing degree in nearly all the subjects examined. A striking familial resemblance was apparent in nearly all particulars, and deviation from normal seemed to follow a fairly harmonious pattern.

CASE REPORTS

Fred Y (I) Ran away from his home in Ireland at the age of 16 years. He fought during the Civil War, during which time he was bitten on the foot by a rattlesnake. Since that incident to the day of his death at 82 years, this individual was said to have had a great deal of trouble with his feet. Fred II states that he can remember his mother, during his childhood, bathing and dressing his father's feet.

After the Civil War, Fred Y I lived for a time in Missouri, then moved to Texas where he married and reared a family.

Fred Y (II) April 24, 1936 to June 8, 1936. This 56-year-old man first noticed trouble with his feet 12 years prior to the above date, at the age of 44 years. He believed, however, that his feet had always been numb.

One evening on removing his shoes he noticed a blister on the tip of the fourth toe of the left foot. No special attempt was made to keep this area clean, and infection occurred. The toe became dark in color, and a foul discharge exuded from an ulcer which formed at the site of the blister. Complete healing occurred in about two months.

He was free of difficulty until two years later, at which time a blister followed by an ulcer appeared on the tip of the fourth right toe, the toe turned black, and the nail became loose and was removed. It was six months before healing occurred.

About one year later he experienced a burn on the right great toe while warming his feet on the kitchen stove and, although there was no pain or burning sensation the burned area became a deep infected ulcer which required six months to heal. Small particles of bone sloughed out through the ulcer. There was never any marked degree of pain. On admission to the University of Oklahoma Hospital on April 24, 1936 a deep penetrating infected ulcer was present on the right great toe.

With the exception of the above complaints, the patient had been quite well and did not recall any illness with the possible exception of measles and probably scarlet fever as a child.

*Presented at the Oklahoma State Medical Association, June 21, 1939.

Reprinted from the *Oklahoma State Medical Journal*, Vol. 1, No. 1, 1939, School of Medicine, Oklahoma City.

Systemic History Essentially negative except for loss of weight in the past two years, 160 to 145 pounds

Physical Examination Well developed, well nourished male, 56 years of age, who did not appear ill. He had several carious teeth and marked pyorrhea

Blood Pressure 140 mm Hg systolic and 90 mm diastolic

Abdomen Negative

Extremities Hair distribution normal. Dorsalis pedis and posterior tibial arteries pulsating normally. Good arches were present in both feet. There was considerable disproportion in length of fourth and fifth toes in comparison with the others



FIG 1 *Fred Y II* (October 28, 1936) Photograph shows marked deformity of the right great toe. Relative shortness of the fourth and fifth toes of both feet. Trophic changes.

The right great toe was considerably swollen and had a dusky color throughout. On the medial plantar surface there was a moderately deep clean ulcer, 2.5 cm in diameter, with a slight discharge which had a very foul odor. On the lateral plantar surface there was a deep penetrating ulcer which had a diameter of about 5 cm, also with a very foul discharge. On the lateral plantar surface of the foot about 2 cm from the base of the fourth toe there was a dry calloused ulcer about 1 cm long and 0.5 cm wide.

There was complete anesthesia to pressure, pain and thermal sensations over both feet on both plantar and dorsal surfaces. Pressure sense was unsatisfactory and delayed to a level as high as the knees bilaterally, and pain and thermal sensations were entirely lost as high as the knees.

Knee jerks and Achilles reflexes were present but sluggish even with reënförment.

The hands were normal in appearance and exhibited no neurological findings.

Intradermal injections of histamine showed no reaction below the knees in either leg, although reactions were quite normal on thighs and forearms.

Roentgen-Ray 1 (May 9, 1936) The terminal phalanx of the right great toe showed a moderate osteoporosis. Lateral margin showed a loss of cortex and was somewhat irregular. The joint space was narrowed. Distal half of the first pha-



Fig. 2. *Foot I* (May 11, 1936) Shows marked swelling of the great toe with several ulcers and two deep sinuses with foul discharge. Entire toe bluish in color. Dry callosities in mid forefoot.

lanx of the great toe showed also moderate atrophy and thinning of the cortex. A small bone fragment lay within the soft tissue medial to the terminal phalanx. The terminal phalanx of the fourth toe was small and irregular. There was similar irregularity of the head of the middle phalanx of the same toe. A small irregular deformity of the terminal phalanx of the fourth left toe was present. Roentgen-ray was suggestive of vascular or neurotrophic changes.

The patient was admitted to the hospital where he was given complete bed rest and a continuous infusion for 50 hours at 70 mm. Hg systolic and 20 mm. Hg pressure. He died as a result of a complete occlusion of discharge on the forty-fourth hospital day. The patient was allowed to return for observation in one month.

The patient did not return for observation and was not seen again until July 6, 1937, at his home. At that time the great toe was entirely healed to all appearances. On the medial plantar surface of the right foot, however, there was a large ulcer about 4 cm. in diameter with a very foul discharge, necessitating a change of dressing four or five times a day. He was advised to return to the hospital but refused to do so.

Patient returned to the hospital July 20, 1938, for further observation. At that time no ulcerations were present, but the first and second toes on the right foot were markedly deformed. The distal phalanx was absent in each toe.

Roentgen-Ray 2 (July 20, 1938). The terminal and three-fourths of the proximal phalanx of the great toe were absent. The base of the proximal phalanx showed a somewhat increased density and a somewhat irregular distal contour. There was



FIG 3 *Fred Y* (May 9, 1938). Osteoporosis of the right great toe. Deformity of the phalanges of the fourth toe of both feet. Narrowing of the articular spaces of both great toes.

narrowing of the tarsal-metatarsal joint of the great toe. The distal half of the proximal phalanx and the entire terminal phalanx of the third toe were absent, and there was almost complete absence of the terminal phalanx of the fourth. The interphalangeal joint was irregular. Roentgen-ray findings were consistent with neurotrophic changes in the phalanges.

Daisy Y. This 20-year-old girl was seen January 7, 1936, at which time she complained of sores on the feet, accompanied by marked coldness and numbness in both lower extremities.

She had noted that her feet were constantly cold, and only in extremely warm weather had they ever been warm and comfortable. They had always had a rather numb feeling, and were never very susceptible to painful sensations.

Lesions first appeared on the feet at the age of 16, when a clear blister became evident on the medial plantar surface of the right foot. There was no history of in-

jury, but infection and lymphangitis appeared, followed by local necrosis and a foul discharge. Four months were required to heal this lesion.

The feet became progressively more numb during the next three years. No more

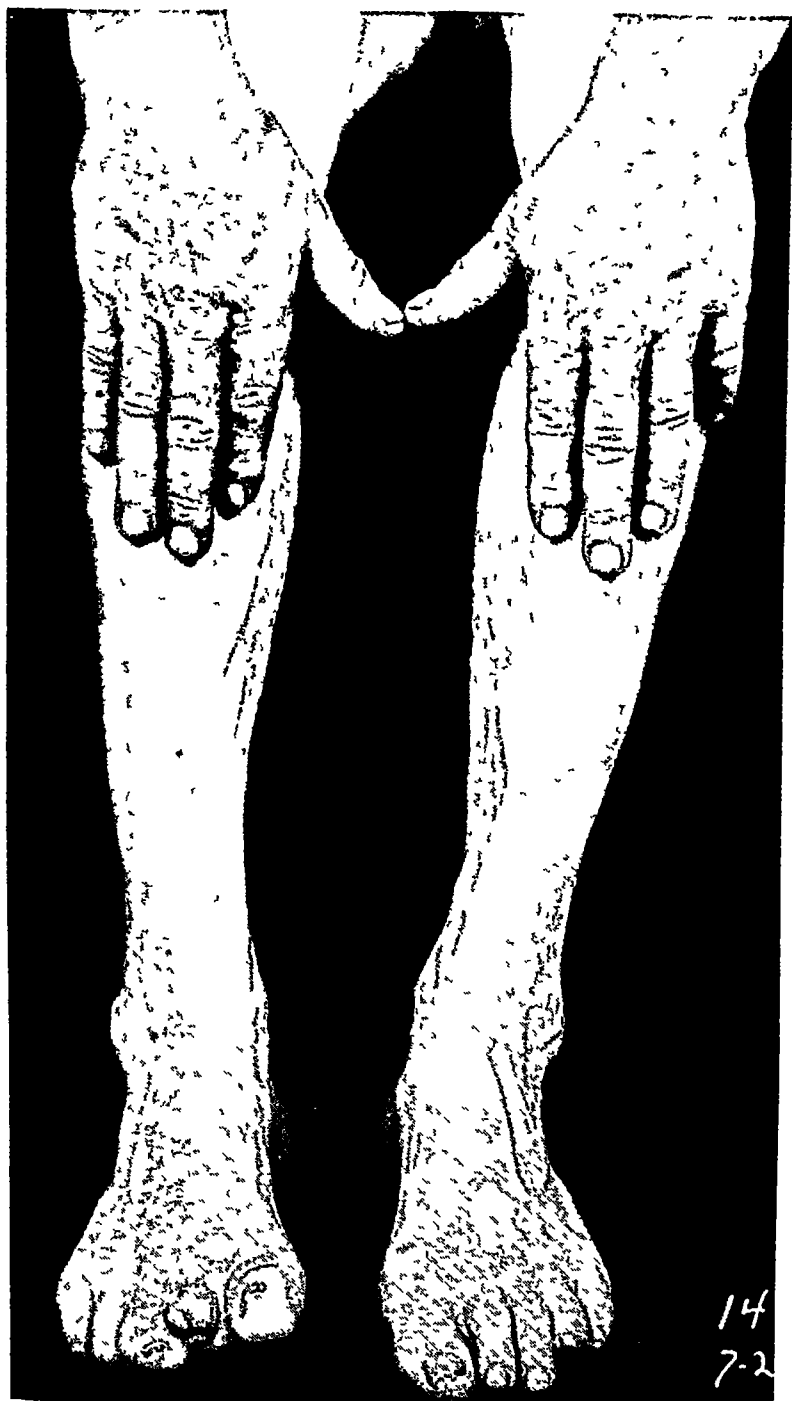


FIG 4 (July 20, 1938) Photograph shows marked deformity of first and second toes of the right foot. There were no ulcers present at this time. Marked nail changes are shown.

skin lesions appeared, however, until January 1935, at which time blisters occurred on the medial plantar surface of the right great toe. The area around them became discolored but not painful, and an ulcer appeared which gradually grew larger and deeper, resisting all attempts at healing. Five months later a similar area became

involved on the left great toe which went through the same course and was equally stubborn in healing. Both lesions persisted up to this time of admission.

Systemic History Negative

Menses Onset at 19 years of age, regular every 24 days, moderate flow. No intermenstrual bleeding or discharge.

Physical Examination Well developed, well nourished young woman of 20 years, weight 100 pounds, height not recorded.

Extremities Grossly negative except for large ulcers on the medial plantar surface of both great toes. These were rather deep and had a thin foul discharge (Figure 7). A bluish discoloration surrounded these areas.



FIG 5 *Figd Y* Deformity of several of the toes on the right foot and shortening of the fourth and fifth toes on the left. This latter is apparently congenital.

The feet were cold and moist; the dorsalis pedis and posterior tibial arteries were pulsating, bilaterally. No marked change in color on elevation or dependency.

Knee jerks and Achilles reflexes were absent bilaterally even with reinforcement. Pressure sense, vibratory sense and position sense were present, but pain and temperature sense were absent bilaterally from distal portion of the lower legs.

Roentgen-Ray (January 7, 1936) No pathologic findings as to blood vessels or bone.

Blood Count Hemoglobin, 80 per cent, red blood cells, 4,400,000, white blood cells, 8,000, neutrophils, 64 per cent, small lymphocytes, 36 per cent, spinal fluid, Wassermann and Kline tests negative, lymphocytes 2, globulin negative.

Course in Hospital Absolute bed rest with heat cradle over both legs was ordered. Forty-eight hours of vasomotor treatment, 60 mm Hg suction and 20 mm

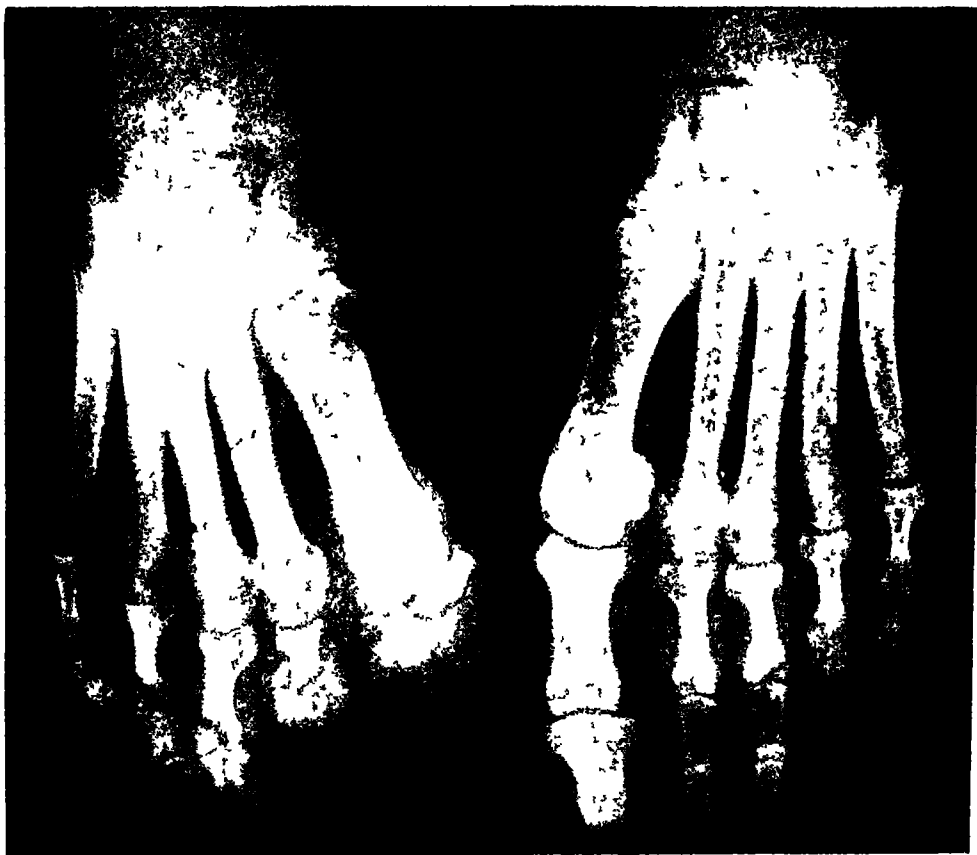


FIG 6 *Fred Y* (July 29, 1938) Absence of several phalanges of the first to fourth toes on the right foot with irregularity of articular surface of the great and fourth toes



FIG 7 *Daisy Y* (January 23, 1936) Ulcers on the medial surface of the great toes. Foul discharge. Immediately surrounding these lesions, the skin has a bluish discoloration. Healed ulcer present on lateral plantar surface of the left foot.

Hg pressure were given during her stay in the hospital. Right foot heated (96° to 100° F) during treatments.

On discharge February 27, 1936, complete healing had occurred.

This patient was not seen or heard of again until she was admitted to the Los Angeles County Hospital on April 21, 1938 complaining of cold clammy hands and feet and ulcers on both feet of one year's duration. The systemic history was negative.

The hospital report disclosed the following description of the extremities. There was a deep necrotic painless ulcer at the base of the left great toe. The entire plantar

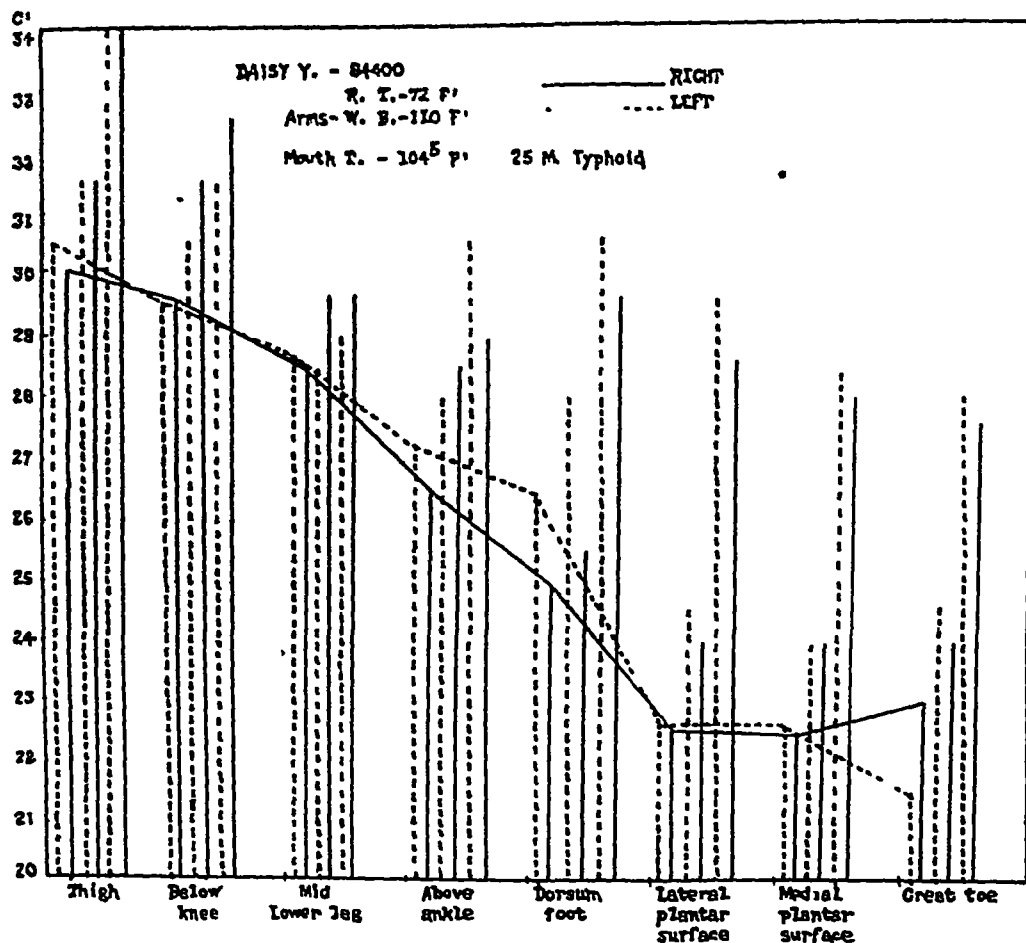


FIG 8 Daisy Y (January 23, 1938) Marked difference in temperature readings between thigh and feet. Moderate rise in temperature is shown by reflex vasodilation (Landis) and greater rise after intravenous injection of typhoid vaccine. This reaction suggests marked vasospasm.

surface was reddened and slightly edematous. There was some red streaking on the medial surface of the leg, and slight left inguinal adenopathy with local tenderness. Dorsalis pedis and posterior tibial arteries pulsated normally.

The note of a neurological consultation mentioned cool perspiring hands and feet, hypesthesia of all the fingers and lower extremities from the knees distally, and impairment of touch sensation bilaterally to above the ankles. Position and pressure sensations were unimpaired. No motor weakness. No pathological reflexes. The consultant noted that he could not palpate the dorsalis pedis or posterior tibial arteries on either foot. There was scleroderma about the toes.

She was discharged from this hospital on June 3, 1938, before completion of the diagnostic study and treatment because she was not a legal resident of California. She was advised to return to the University of Oklahoma Hospital for further observation and treatment.

Rachel Y June 21, 1938 to July 20, 1938 The patient was first seen in the outpatient department on February 27, 1935, at the age of 16, at which time she was

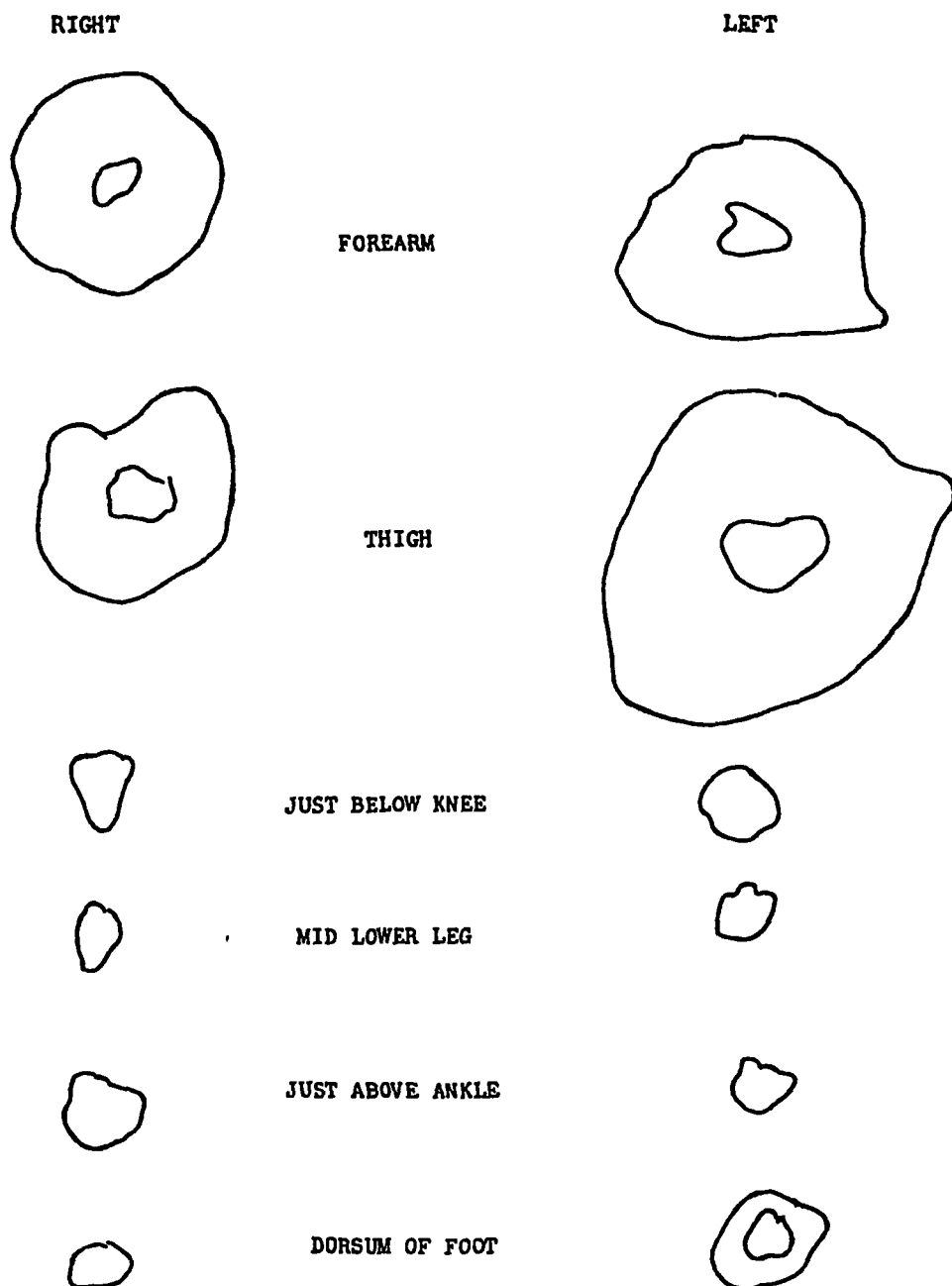


FIG 9 *Daisy Y* Histamine flares 1-1000 histamine chloride solution intradermally

complaining of amenorrhea and a purulent vaginal discharge. A diagnosis of non-specific vulvo-vaginitis was made, which responded well to treatment.

She was seen again June 21, 1938, when the following story was obtained:

Ever since childhood the patient had been conscious of marked sweating of the feet to such a degree that she could at almost any time "wring water from her stock-

ings" Because of this condition she preferred going barefoot when at all possible During these times she cut her toes many times, causing bleeding but never pain Until the last few years she was able to appreciate pain elsewhere on the feet and extremities but she believed there had been a gradual spread of numbness and anesthesia, finally involving both feet in their entirety

Paresthesias were frequent, she at times had a feeling that stickers were present on the soles of her feet a sensation so real that she occasionally removed her shoes and stockings in order to examine her feet

Feet were cold to touch at all seasons When exposed to moderate cold, feet and hands turned white, then blue and finally, on warming, became quite red Aching was present in the arms when these were cold Nails had had a tendency to turn black occasionally at which time they broke quite easily She had considerable difficulty in



FIG 10 Daisy Y (February 25, 1936) Approximately one month after admission Heat cradle, vasculator treatments and absolute bed rest Ulcers are almost completely healed

walking at night, and stumbled and bruised her toes and shins when she made the attempt

About one year prior to admission a clear blister appeared without known provocation, on the medial plantar surface of the left great toe Most of the toe became very pale except at the base, where the skin showed a dark blue discoloration An ulcer with a foul discharge soon appeared at the site of the blister, lymphangitis followed, and finally marked left inguinal adenopathy Alcohol dressings were applied, and the ulcer healed in about 10 weeks

Systemic History Negative except for late onset of menses at 17 years of age

Physical Examination Fairly well developed, well nourished girl of 18 years She did not appear ill Weight 105 pounds Span 66 inches Height 65 inches

Extremities Appeared normal except for a ragged unhealthy appearance of the toe nails The feet and hands were cold and clammy Large beads of perspiration were present on the feet

Dorsalis pedis and posterior tibial pulsation were absent bilaterally on several examinations. There was complete anesthesia to all sensations in all the toes. Tactile sensation was present but reduced, pain and thermal sensation were absent over the distal half of the lower legs. Only extremes in heat and cold could be felt from this region up to the knees. Sensation elsewhere on the body was normal. Vibratory sensation was reduced below both knees. The sense of position of the big toe



FIG 11 *Daisy Y* (July 19, 1938). Ulcer present on junction of great toe and plantar surface of foot. Foul discharge. Deformity of second toe shown. (Photograph through courtesy of the Los Angeles General Hospital.)

was inaccurate. Heel to knee test showed marked ataxia bilaterally. She stumbled a great deal when walking with eyes closed. There was pastpointing on the finger-to-nose test. Romberg station was unsteady. Deep reflexes were present and active.

Arthur L Y, Aged 48. This patient was examined at his home on July 10, 1938. He had been perfectly well until the spring of 1918, while serving with the A E F. A blister then appeared on the medial plantar surface of the right great toe, which was not

preceded by trauma. The patient was treated at the infirmary. He wore a cutout shoe, and healing occurred in about six weeks. He was free of any trouble thereafter until 1921 when a blister appeared in that same location, requiring about a week or so to heal. There was no recurrence until March, 1923, when a blister, followed by a deep ulcer, appeared on the tip of the fourth toe of the left foot, making hospitalization necessary for several weeks. On his discharge he was advised to use crutches until healing was complete. This required five months.

In November 1923, a large 'black blister' the size of a silver dollar appeared on



FIG 12 *Daisy I** (July 19, 1938) Reading. Considerable alteration of the structures of the phalanges of the great toe bilaterally. In the right foot there are punched out rarefied areas adjacent to the joint spaces between the phalanges. Joint surfaces are extremely irregular and are separated by an interval. The left great toe joint space is practically obliterated and the areas of rarefaction are less sharply defined. Considerable soft tissue swelling about both great toes. W. L. Stittson, M.D. (Through the courtesy of the Los Angeles General Hospital.)

the lateral plantar surface of the left foot. This became gangrenous in about four days. A surgeon excised the gangrenous area on the sixth day. Five months were required for healing.

Since then, except for nearly the entire year of 1936, when he was resting, the patient had never for more than 30 days at a time been free from blisters, followed by indolent ulcers requiring long periods of time to heal.

During the winter of 1926, the entire right foot was covered with blisters, superficial sloughs and discharging ulcers of various sizes, many of them confluent. About three months later similar lesions of the same extent appeared on the left foot.

The feet were exceedingly painful. Nine months were required for healing. During this time he was given a course of salvarsan and mercury, although repeated negative blood Wassermann tests had been obtained. No improvement resulted from this treatment.

In 1930 a roentgen-ray examination showed extensive osteomyelitis involving the bones of the right foot. Several minor operations were undertaken and small segments of bone removed. Several large ulcers discharging sero-purulent material were

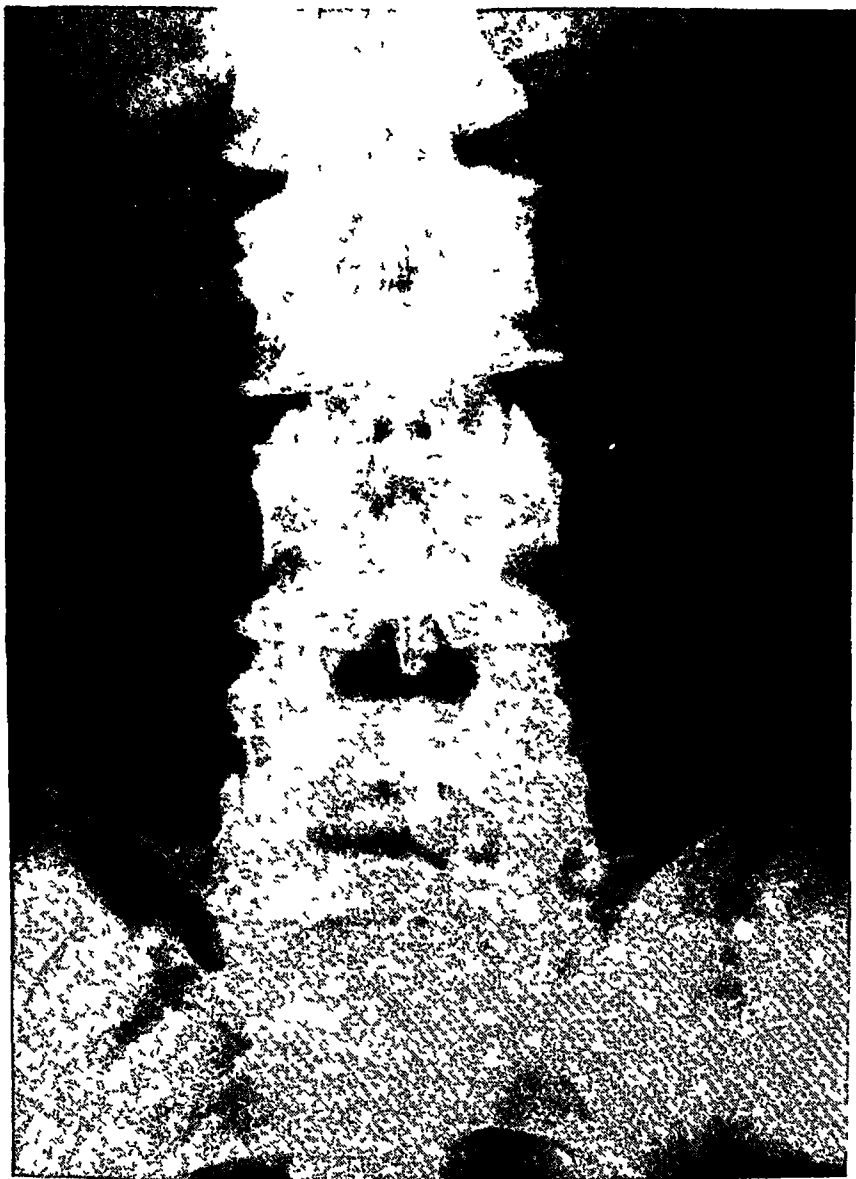


FIG 13 *Rachel Y* (August, 1938) Spina bifida occulta

present on this foot and continued to be present until 1935, when the entire lower leg became insensitive to pain or touch. A Gritti-Stokes amputation was done at a Veterans' Hospital during that year.

Owing to the enforced rest following amputation of the right leg the left foot became completely healed, was painless, and was free of any trouble for the entire year of 1936. In November 1936, however, while standing on a ladder, the patient had a feeling of "something breaking" in the left foot accompanied by moderate pain. On examination he found on the ball of his foot a large blister which rapidly changed

into a deep ulcer discharging foul material. Since then dressings have been required twice daily. If he rests in bed for several weeks the lesion almost entirely fills in with tissue but if weight is again placed on the foot the lesion breaks down and a deep discharging ulcer appears. At present he feels fairly well, but must apply four to five dressings to the foot daily.

No paresthesias or hyposensitivity in the extremities were noted until 1928, when the patient found that he had to watch where he placed his feet in walking. Shortly after this he began to notice that he was insensitive to all but extremes in tempera-

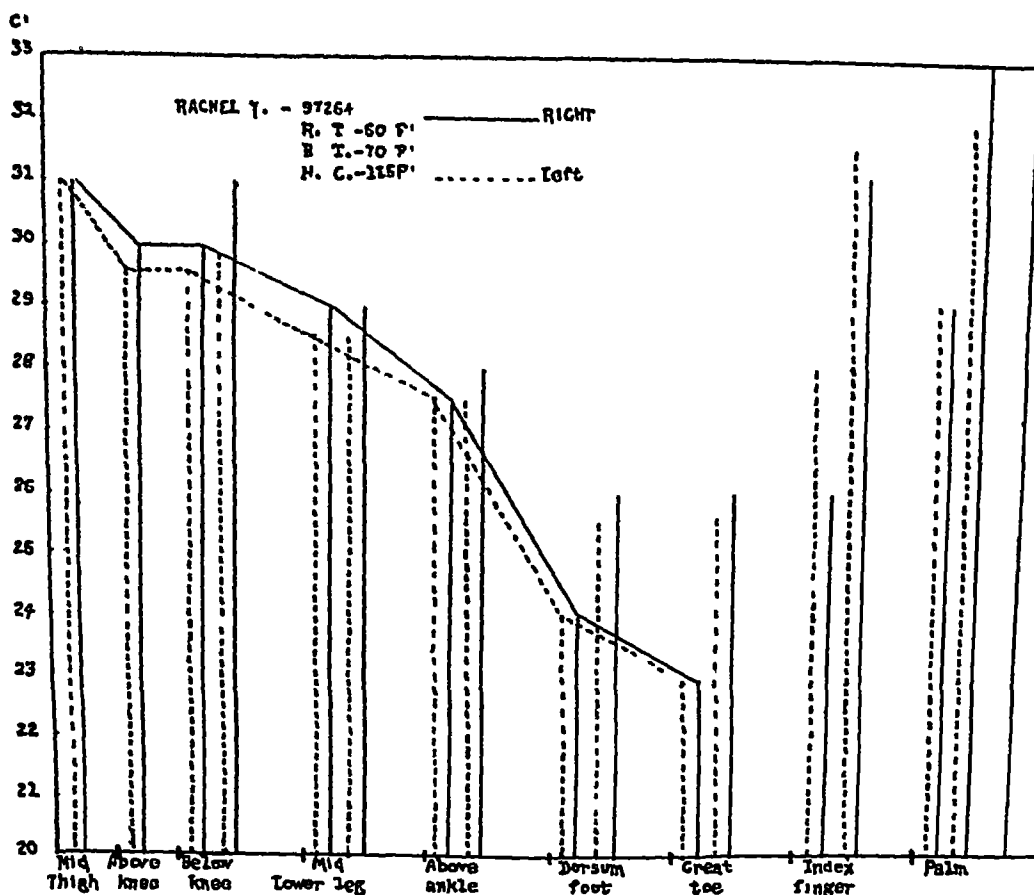


FIG 14 Rachel Y (August, 1938) Shows marked difference in temperature between the thigh and foot bilaterally and relative coldness of the distal halves of the lower extremities. Vasodilatation and increase in temperature are shown after the body has been enclosed in heat cabinet, temperature 115° F with extremities exposed at 76° F.

ture either hot or cold, and he had difficulty in interpreting which of these was present. This difficulty was noticeable only in the feet and lower legs.

Systemic History Negative except for nocturia two to three times and day frequency three to four times with some little difficulty lately in starting the stream. Weight varied very little, averaging 130 to 135 pounds.

Past History Measles, mumps, typhoid in childhood. Pneumonia at 15 years of age. Malaria in 1917. Appendectomy and herniotomy in 1934.

Physical Examination Well developed but not well nourished man, 48 years of age. Did not appear ill. He was ambulatory, used crutches and had an artificial limb on the right. The left foot was swathed in bandage material.

Extremities Right leg amputated at the knee joint, the stump was in good condition, the musculature of the thigh atrophic

Left leg, complete anesthesia below the mid-lower leg Achilles reflexes and knee jerks were hypoactive, plantar reflex absent

The toes were deformed and atrophic and there was a large ulcer, about 2" by 2" on the ball of the left foot, which had a foul seropurulent discharge No hypesthesia

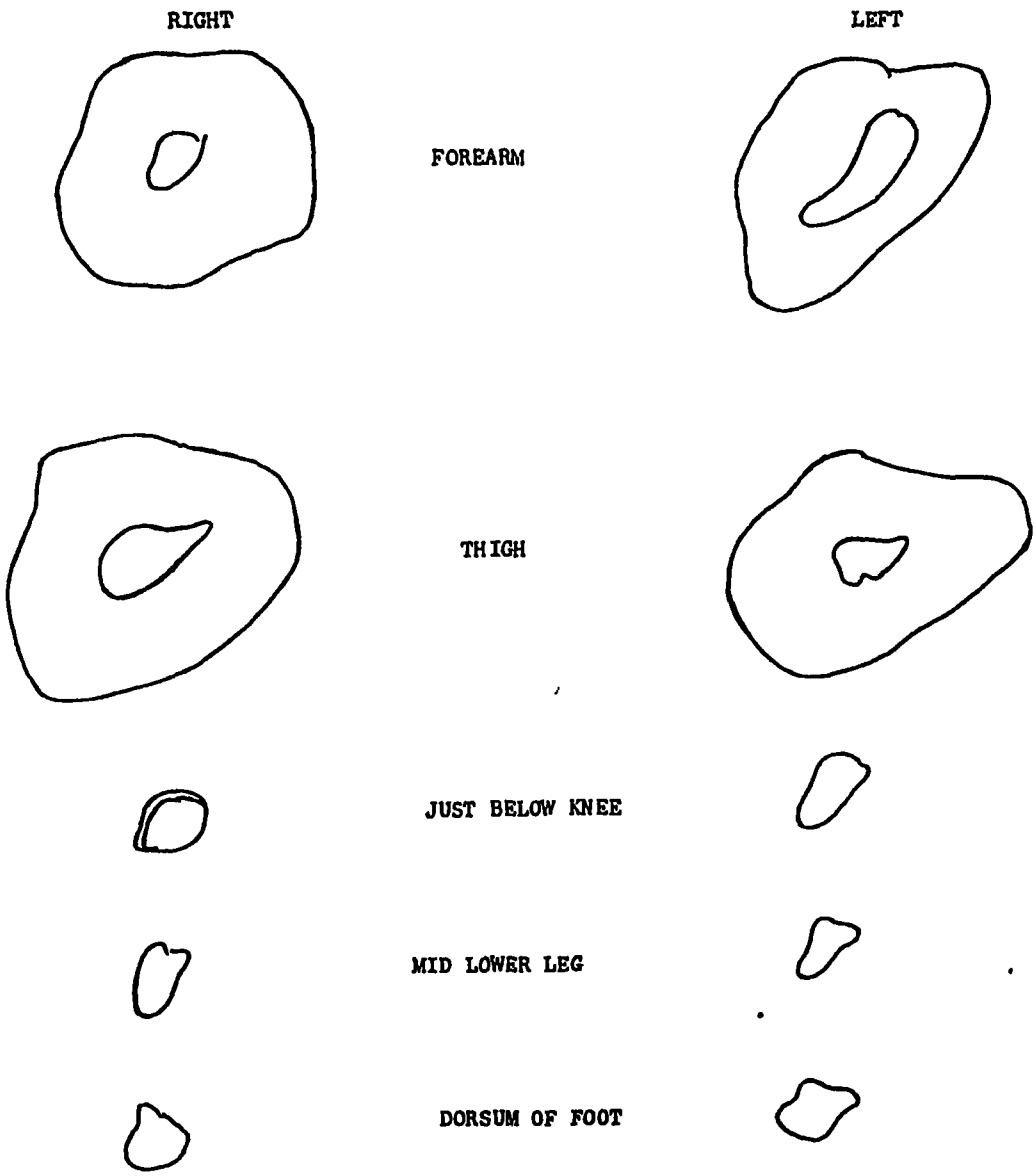


FIG 15 Rachel Y Histamine flares 1-1000 histamine chloride solution intradermally

was noted in the hands The biceps and triceps reflexes were active (plus two), and the Hoffman reflexes were negative

James A Y Aged 16 This boy was examined at his home on June 10, 1938 He had apparently been a normal and healthy child until the age of six years but had not been very well since that time At this age he had a severe attack of measles complicated by pneumonia and heart trouble

At the time of his examination he had considerable dyspnea on exertion and developed obstinate chest colds and bronchitis very easily There had never been any noticeable cyanosis or edema Systemic history was otherwise negative

This boy noticed painful white hands and feet on exposure to extreme cold, which changed to a bluish red on warming. He stated he had never observed any difficulty in appreciating heat and cold nor had he observed insensitivity to pain. His feet tingled and went to sleep very easily and a blow or bruise was followed by anesthesia of the affected area for several minutes.

Physical Examination Poorly developed and poorly nourished boy, 16 years of age. Somewhat retarded, but cooperated well.

Head and Neck Scalp was negative. Eyes pupils reacted normally. Teeth were good. Tonsils were hypertrophied. High arched palate.

Chest Respiratory excursions equal and symmetrical. No areas of impaired resonance.

The point of maximum impulse was 13 cm from the midsternal line and was diffuse. Percussion showed the heart border extending to the axillary line.



FIG 16 *Arthur Y* (June 10, 1938) Deformity and displacement of the fifth toe of the left foot owing to secondary infection and loss of bone.

A systolic and diastolic murmur could be heard at the base and at the seventh interspace on the right near the sternal border. The diastolic murmur could be heard along the left sternal border between the third and fifth intercostal spaces.

Blood Pressure Right 140 mm Hg systolic and 80 mm diastolic. Left 135 mm Hg systolic and 80 mm diastolic.

Popliteal Blood Pressure 150 mm Hg systolic and 80 mm diastolic, and equal bilaterally.

Abdomen Negative.

Extremities Negative except for marked painless flat feet. There was no clubbing. He was unable to appreciate any but extreme thermal changes. Pain sensibility was reduced on the soles of the feet, intact on the palms. The dorsalis pedis and posterior tibial arteries were pulsating normally.

Reflexes Normal reflexes present and active, no abnormal reflexes elicited.

Virginia Y Aged 17 The patient was examined at her home on June 10, 1938. She had always had good health except for a severe attack of scarlet fever at seven years of age. She had noted as long as she could remember that her feet would sweat a great deal and that two or three changes of stockings daily were necessary for comfort. She had also constantly suffered with cold feet. When exposed to cold both hands and feet would turn dead white and remain so until warmed artificially, whereupon they turned a reddish blue and became quite painful and throbbing.



FIG 17 (Above) *Murrel Y* (June 10, 1938) Painless flat feet, marked
 FIG 18 (Below) *James Y* (June 10, 1938) Painless flat feet, marked

For three or four years prior to examination she noticed that she was quite apt to burn her hands if she was not very careful. Once when testing an iron for heat she placed the palm flat against the ironing surface and felt very little warmth, but later in the day a large blister appeared, covering the entire surface, and the hand was stiff for many days.

She experienced marked difficulty in walking, especially in the dark, when she was very apt to stumble and bruise her feet, and even during daylight she had to be more or less aware of where she placed her feet. When walking a considerable distance the feet would burn a great deal, yet when she palpated them they were noticeably cold and wet.

Bruises and blows to the feet resulted in anesthesia to the affected area for hours afterward. She was frequently troubled with blisters on both feet, but none was present at this time. There had never been any ulcers on the feet.

Systemic History Negative except for late onset of the menses at the age of 17.

Physical Examination Well developed and nourished girl, 17 years of age, intelligent and cooperative. There was a slight diffuse enlargement of the thyroid.

The blood pressure was 120 mm Hg systolic and 80 mm diastolic.

The extremities were superficially normal in appearance.

The biceps and triceps reflexes were hyperactive (plus two). The knee jerks and Achilles reflexes were obtained with reinforcement. The plantar reflexes were positive.

The position sense of the big toe was inaccurate bilaterally.

There was an irregular response to heat and cold stimulation on the dorsum of the

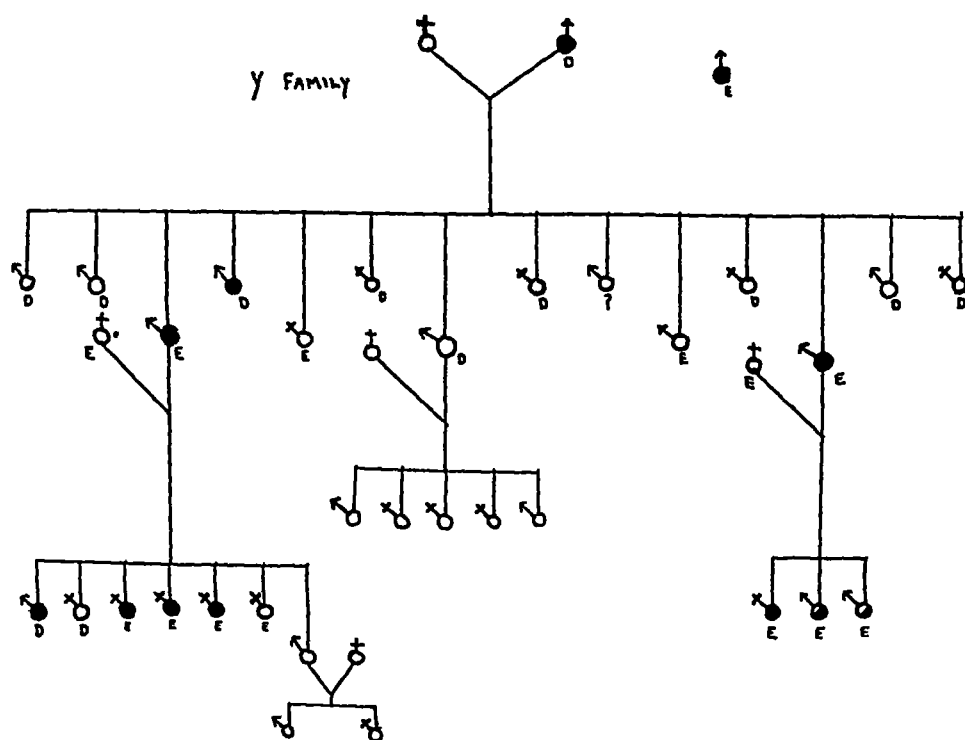


FIG 19 Family tree. Blackened areas indicate individuals with the disease, confirmed either by examination or through family history. The letter (E) indicates those examined.

feet and lower legs and dorsum of the hands. Application was slow. Pain sense was likewise irregular. The soles of the feet and the palms of the hands were insensitive to thermal and painful stimuli, but were sensitive to pressure.

The hands and feet were cold and clammy.

F Y S, 33, married, housewife. This 33 year old woman was seen for the first time in the outpatient department of the University Hospital on February 5, 1936. The following history was obtained:

She had been well until four years before, at which time she noticed a painless blister on the ball of the right foot. This lesion subsequently ruptured, and the underlying tissue became infected and discharged very foul material. She consulted a physician who apparently removed some necrotic tissue. The lesion was very slow in healing, requiring six months, three of which were spent on crutches.

About three months later a blister appeared on the medial plantar surface of the big toe of the right foot. This became infected and was followed by lymphangitis and right inguinal adenopathy. Gangrene soon occurred, necessitating removal of the distal half of the toe. Eight to ten months were required for healing. During the latter months of this process the large toe on the left foot became similarly involved and blisters, followed by gangrene, became evident on the tips of the four smaller toes.

Since the onset the patient had never been free of trouble. There had been a succession of blisters, followed by lymphangitis and ulcer formation, which required months to heal. These were always on the plantar surface of the toes and distal half of the feet.

The patient had noted for the past four years that her feet had a dead feeling and that she was able to appreciate only extremes in heat and cold, and then only after exposure to these temperatures for some time. During this period she had burned her feet on several occasions, resulting in slow-healing painless ulcers. During the last few months there had been considerable pitting edema of both feet. There were no seasonal variations in degree of involvement. The fingers were numb at times.

Systemic History Negative except that menstruation was late in onset, at 20 years of age.

General Physical Condition Negative. Pulse, 80. Respirations, 20. Temperature, 98.4°.

Extremities Grossly normal in appearance except for loss of the distal phalanx of the right great toe and distal phalanx of both small toes. There was a foul discharging ulcer at the site of the proximal phalangeal joint of the right great toe. To palpation there was a marked difference in temperature between the thigh above the knee and the foot. Bilaterally, the temperature decreased rapidly as palpation was carried from the knee to the foot.

There was hypesthesia of both lower extremities from mid-lower leg downward and of the palms and dorsa of the hands bilaterally. The feet were practically anesthetic to pain and thermal stimulus. Response to pressure stimulus was slow and not very clear. The position sense of the big toe was unstable but fair. There was slight ataxia in the heel to knee test bilaterally. Vibratory sensibility was reduced.

No pulsations could be felt in the dorsalis pedis arteries of either foot. The posterior tibial artery was faintly pulsating on the right, not felt on the left.

Treatment Complete rest in bed was impossible though the patient was advised to obtain as much rest as possible. Thirty-four hours of vasomotor treatment were given with suction 60 mm Hg, pressure 20 mm Hg. Considerable objective and subjective improvement was noted on discharge, March 19, 1936, although the ulcer was not healed. From the date of discharge on March 19, 1936, the patient was not seen again until June 13, 1938, at which time she was examined at her home in Long Beach, California. Physical and neurological findings were much the same as on discharge. There was a deep ulcer about 2 by 2 cm on the medial surface of the right great toe, which had been present for several months. The patient stated that several fragments of bone had sloughed from this area. Roentgen-ray was not available.

SUMMARY OF FAMILY HISTORY

The individual representing the first generation of this family, as far as this record is concerned, has been dead many years. He was not examined, but the evidence is strong, from the information given by the members of the second generation, that this man had a severe disease of the feet throughout the greater part of his 81 years of life.

Of 14 members of the second generation, only five are living, three of these have been examined by us and one by Dr. Lee Rice of San Antonio, Texas. Two of this generation, examined by us, and Cora, examined by Dr. Rice, are apparently free of the affliction. There is strong evidence, from the family, that David, another member of the second generation, died with gangrene of the feet. He had not been examined, however, nor have we been able to obtain any medical report concerning him.

Of questionable importance in this group is the history of two other members dying of diseases referable to the nervous system, namely, Charles, who died of paralysis, and Gemma, who died of meningitis. This may have been coincidental.

In the third generation, seven of a possible 15 individuals have been examined. Five of this generation, the children of Charles, are to date untraceable. John, a son of Frederick, is unavailable. Leona, a daughter of Frederick, died of appendicitis at the age of 12. There is no history of her having had the disease. David, another son of Frederick, died with a peculiar foot affliction with gangrene at the age of 13, but a medical history is lacking. Gracie Y., a daughter of Frederick, had a typical history and findings of anterior poliomyelitis, but examination was fruitless in her case for purposes of this report.

Of the six remaining members of this generation all have shown some degree of dissociation of sensibility in the feet. Some have exhibited changes as high up as the knees. Two have had impairment of sensation in the hands. Although the loss or decrease of pain and temperature sensibility is the most important neurological finding in these patients, four of those examined showed some disturbances in the sense of position.

Purposely left out of the individual reports were some findings common to all patients examined in both generations except the two women in the second generation. All appeared to have been poured from a common mold. All were tall and thin, and the span averaged $\frac{3}{4}$ inch more than the height in all in whom this particular finding was checked. The hands and feet were narrow and long, the fingers, except in Murrel, son of Arthur, were long and slender. All had high arched palates. Two had a moderate pes cavus and two had marked painless flat feet. The scapula in all had a definite tendency toward winging. Murrel, aged 14, had no dissociation of sensibility, although marked deformity of both little fingers was present.

Four of the third generation, three girls and one boy, gave histories quite suggestive of Raynaud's phenomena, although attempts to precipitate these symptoms in one girl, Rachel, were not successful in our laboratory.

Nearly all of the individuals examined showed evidence of circulatory inadequacy in the feet and lower legs. Histamine flares were markedly reduced below the knees in the three to whom this test was given. The vasomotor gradient was steep both clinically and on laboratory examinations in all those in whom infection was not of sufficient magnitude to change the local temperature.

Six of the individuals examined have had painless slow-healing ulcers of the feet. Three gave a history of bone sloughing from these ulcers. Two gave a history of self-amputation of some of the toes. One had had an amputation at the knee-joint because of deformities and osteomyelitis.

Roentgen-Ray Trophic changes were present in the bones of the feet in two patients, and there was evidence of loss of bone structure in the phalanges. In one patient, a roentgen-ray of the lumbar spine was taken disclosing a spina bifida occulta.

In three patients there was a late onset of menses at 17, 19, and 20 years.

COMMENT

Before presenting these cases we made a careful search of the literature, in order to unearth, if possible, reports of a familial condition which though resembling syringomyelia, is yet of a more static nature. It seems to represent a constitutional abnormality of which syringomyelia remains, so to say, one potentiality, but which may find partial expression in the most varied local anomalies and clinical manifestations, which have not the progressive character of that syndrome.

Syringomyelia has long been recognized as a chronic progressive process in the spinal cord, the result of glial proliferation which leads in time to necrosis and cavity formations in that organ. The results of this progressive gliosis are then expressed in typical progressive atrophies and sensory disturbances affecting various parts of the trunk and extremities, according to the particular localization of the original cord lesion.

In syringomyelia proper, the most characteristic location of the lesion is the central portion of the cord. A lesion so placed will interfere with the decussating fibers carrying pain and temperature sensation, and a decrease or complete loss of sensibility will occur in the region in which these fibers originate. The sensory loss will be on only one side if the lesion affects the posterior gray horn on that side, but on both sides if the commissure is involved. Extension into the anterior horns will cause weakness of the muscles in the segmental distribution. The pyramidal tracts are sometimes involved, in which case a spastic type of paralysis may ensue.

Reports in the literature of the English language are rather meager concerning the condition status dysraphicus, which is now generally accepted as the constitutional substratum underlying syringomyelia. With this in mind, we are reporting the above patients as representing either a strong familial tendency toward syringomyelia, or, what is more likely, as examples of status dysraphicus, a similar and probably closely allied condition, but one showing evidence of widespread vasomotor and trophic disturbances of more varied kinds than the former, and exhibiting little of the tendency to progress, which has long been recognized in syringomyelia.

Considerable debate has arisen with reference to the familial appearance of syringomyelia, some authors denying that this affection is congenital and

insisting that if it appears more than once in a family group this is a pure coincidence without heredo-biological significance

Schlesinger,¹ who wrote an authoritative work on the subject of syringomyelia in 1902, in which he discussed 260 cases of this condition, referred to several reports of what were claimed to be familial cases of syringomyelia. These were the cases of Ferrannini,² Nalbandoff,³ Pieobrajenski,⁴ Krafft-Ebing⁵ and of Verhoogen and Vandervelde.⁶ Schlesinger entirely rejected these reports, of which only the last-named reported autopsy findings, and insisted that there is no such thing as congenital syringomyelia, hence, any so-called familial cases were of no interest. In the case of Verhoogen and Vandervelde he said that it was probably not syringomyelia. Here the condition affected two adult sisters and one brother who were children of alcoholic parents, and thus inherited a congenitally inferior nervous system. The disease came into manifestation insidiously, at the ages of 8, 12 and 12 years, respectively, unobserved at first by the patients, but followed by a long history of trophic disturbances in muscles and nails, cyanosis of limbs, livid and cold hands and feet, and the classic thermo-anesthesia of syringomyelia in high degree.

In 1903, Bruns,⁷ reviewing these earlier cases, reported one of his own in which four of five children of healthy parents had deep symmetrical gangrene of fingers and toes, with ulcers of the feet and dissociation of sensibility. He regarded this as a case of familial syringomyelia in the lumbar spinal cord. In each of these four individuals the symptoms had first been observed at about the age of 17. The condition was progressive, and in two of the cases amputation was later necessary.

Fuchs,⁸ in 1903, was the first to give the name "myelodysplasia" to a syndrome which, he said, is a *pictur*e of syringomyelia, but without progression. In association with Mattauschek⁹ he found the following characteristics present in myelodysplasia:

- 1 Weakness of the sphincters, enuresis persisting into adult life
- 2 Syndactylism of the second and third toes
- 3 Disturbances in sensation of the legs, of a dissociated type, in which thermo-anesthesia is most marked
- 4 Cleft arches of one or more vertebrae
- 5 Abnormal skin and tendon reflexes of the abdomen and lower extremities
- 6 Deformities of the feet, clubfoot or flatfoot, often associated with trophic and vasomotor disturbances
- 7 Skin changes, such as hypertrichosis, naevus and fovea coccygea

To these, Bremer¹⁰ later added the following:

- 1 Acrocyanosis of the extremities, especially of the fingers
- 2 Crumpling of fingers, especially the little fingers
- 3 Sternal anomalies, particularly infundibular thorax

- 4 Inequality of the mammary glands
- 5 Kyphoscoliosis
- 6 Greater span than height

While not all of these manifestations were present in every case of myelodysplasia, Fuchs⁸ observed a striking tendency for several of them to be associated together in individual patients. He attributed the condition to a "congenital hypoplasia or dysplasia of the lower spinal cord." Mattauschek at the same time observed that in five-sixths of his cases, enuresis was the expression of an abnormality of the lumbar spinal cord, and not due to a psychic component as had been maintained. It was often accompanied by syndactylia, abnormal patches of hair, disturbed reflexes and hypesthesia for heat and pain. This myelodysplasia, this "syringomyelia without progression" was, as we shall soon see, synonymous with the status dysraphicus that was to be differentiated from syringomyelia by Bremer¹⁵ nearly 20 years later.

In this same year (1909) Clarke and Groves¹⁰ reported a familial case of sacrolumbar syringomyelia in a brother and sister aged respectively 23 and 15. Here the phalanges and metatarsal bones had undergone a process of atrophy and were found to have gradually disappeared.

Haenel,¹¹ on the basis of these various publications which showed the indisputable existence of syringomyelia with familial trophic disturbances, asserted that such degenerative stigmata as spina bifida, ear lobe anomalies, cervical rib, duplication of the central canal, meningocele, microgyria, and the like, prove that many patients have already brought along an anlage of syringomyelia, and also that there are rare cases of congenital gliosis. Further evidence of this congenital factor was produced when Lundgaard¹² observed (1913), a seven months' fetus, which was born with only one of its four limbs present, and with various other dystrophies. The child was autopsied nine weeks after birth, at which time the type of morphologic changes found in the spinal cord justified a diagnosis of beginning syringomyelia.

In 1919 Bielschowsky and Unger¹³ published the modern conception which no longer recognizes any real difference between congenital anomalies of the gray substance and the central canal, on the one hand, and syringomyelia on the other. Their work was taken up by Henneberg,¹⁴ in 1920, who demonstrated by autopsy of three spina bifida infants who died a few weeks after birth that the changes which bring about syringomyelic cavity formation begin very early, plainly in the intrauterine period, and that syringomyelia may be conceived as having its basis in a rudimentary form of spina bifida.

He suggested that the congenital anlage is probably very common, and is *inherited*, but that very special exciting factors are necessary to arouse active gliotic proliferation. It seemed clear that a faulty closure of the neural tube might give rise to the inclusion of embryonic cell rests in the spinal cord, which eventually result in gliosis and finally in cystic cavity for-

mation He felt that this condition of "dysraphy" was responsible for many of the hereditary neurological diseases, and that it was the expression of an hereditary degeneration

In 1926, Bremer¹⁵ introduced the name *status dysraphicus* and published an epoch-making work on the subject Here he placed on record his findings in 10 families in which he made an intensive study of heredodegenerative states, among which were the results of his studies in four cases that came to autopsy As de Vries,¹⁶ and later Riley,¹⁷ pointed out, the clinical syndrome of Bremer's status dysraphicus is essentially that already described by Fuchs under the name *myelodysplasia* Bremer made it clear that in order to understand this condition, which is widespread, it is necessary to examine the other members, the healthy individuals, in family groups in which some one member has a sufficiently severe disturbance to bring him to the doctor Most of these dysraphic individuals are living a normal life and do not seek a physician's treatment In a very recent article, Bremer¹⁸ states that he continues to find, in the relatives who are not sick, "formes frustes" of the syringomyelic syndrome—a condition which does not show any progression, but in which vasomotor and trophic disturbances are very evident He has repeatedly pointed out that this status dysraphicus is found not only in syringomyelic patients, but is systematically present in all diseases of the entire group of dysraphic disturbances In the first of his 10 families, in which four generations and 25 individuals could be accounted for, the 15 who could be examined were all found to have the classic symptoms of syringomyelia Most of them were not ill, however, and their stigmata would not have come to light if they had not been definitely looked for

Curtius and Lorenz¹⁹ have gone deeply into this subject, and conclude that dysraphicus is not only developmentally and anatomically, but also clinically, a thoroughly definite constitutional type That the development disturbance is inherited was shown in 13 to 14 cases They studied 32 cases of status dysraphicus and 17 of syringomyelia Of the 32 cases of status dysraphicus 21 had striking nervous abnormalities, and 16 had marked mental disturbances Examining at random 500 roentgenograms of the spinal column out of the archives of their department, they were amazed to find that 17 per cent of normal persons are dysraphic, a figure which Bremer accepts as correct According to these authors, the relations of status dysraphicus go beyond the narrow field of syringomyelia They state that dysraphic symptoms are being seen relatively often in other types of heredodegeneration For example, status dysraphicus is found in many families with cases of Friedreich's ataxia and is frequently met with in patients with multiple sclerosis But it appears, says Curtius, that we do not yet possess the requisite knowledge to systematize these conditions and that we are still unclear with regard to the relation of status dysraphicus to other organic nervous diseases Investigation of the subject is rendered very difficult by the fact that the anatomic changes are accompanied by clinical symptoms in only a small fraction of the cases, so that they are usually an accidental finding

during examination of a patient who comes for some other apparently unrelated condition

Passow²⁰ made the observation in 1934 that under similar conditions point to status dysraphicus. Systematic examination of over 70 patients presenting Horner's syndrome (ptosis, enophthalmos and miosis) showed, astonishingly, that in nearly all the 64 families represented, familial signs of status dysraphicus were frequent. These findings were confirmed by Coppez,²¹ who states that status dysraphicus gives the key to the hitherto unknown etiology of Horner's syndrome.

It is not the dysplasias themselves, says Touraine²² (1936), that are hereditary, but the common foundation, the status dysraphicus which, according to the individual subject, is revealed now by one and now by another of several manifestations, the ensemble of which deserves to be regarded as belonging to status dysraphicus.

Our search of the literature for familial cases of syringomyelia has brought to light some 30 instances of families that have been placed on record in which two or more individuals were afflicted. Among these are those of Bramann,²³ with symptoms in three brothers, of Goldblatt,²⁴ in a mother and daughter, of Price,²⁵ in which four generations shared in a group of similar dystrophies, of Krukowski,²⁶ in a father and daughter, of Karplus,²⁷ in a father and son, of Redlich,²⁸ in two brothers, of Wexberg,²⁹ in a father and son, of Barre and Reys,³⁰ in a brother and sister, of Kino,³¹ in six members of a family group, of Riley,¹⁷ in a mother and six children, of Schultze,³² in three of a family, of Klippel and Feil,³³ in twin sisters, and of Goebbel and Runge,³⁴ who reported a family in which there had been 12 cases of symmetrical gangrene, six of which were fatal. In this family the males alone for three generations had this disease in the lower extremities, feet and toes, beginning at the age of eight to 10 years. Weitz³⁵ observed a case in identical twins. On the other hand, Stahle,³⁶ quoted by H. A. Riley, described twins 45 years of age, one of whom had a definite syringomyelia for about 19 years, whereas the other was quite well. He pointed out that, inasmuch as they were identical twins, the condition was not purely idiopathic.

Recently Van Epps and Kerr,³⁷ counting the individuals involved in these familial cases rather than the number of families, found a total of only 44 individuals on record as having familial cervico-thoracic syringomyelia, and in only four families did the number of such individuals exceed two. The lumbosacral group showed the greater familial tendency, embracing a total of 81 individual cases, 27 of which were subjects of their own report. Of these 27, 26 belonged in four families.

Barraquer and de Gispert³⁸ in 1936 reported 13 individuals in one family characterized apparently by a combination of cervico-thoracic and lumbosacral abnormalities. They think no other report has found 13 afflicted subjects in two generations, as here.

Few of the reports in English have discussed the so-called stigmata of degeneration on dysgenesis present in status dysraphicus. It seems there

is little difference in the patients reported by Riley as probable victims of status dysraphicus and those of Van Epps and Kerr who prefer the term lumbo-sacral syringomyelia. Smith's³⁹ six patients who had what he chose to call "a familial neurotrophic condition of the feet with anesthesia and loss of bone," closely resemble the patients as presented by Van Epps and Kerr, and our own patients.

From a practical point of view, there does not seem to be any particular reason why the two syndromes should be considered separately, unless one wishes to refer to status dysraphicus as a "microform of syringomyelia" (Passow), a disease more familial in tendency, exhibiting slower progress and consistent with a fairly active, useful life. The majority of reports of cases of true syringomyelia point out its slow, insidious progress. Curtius⁴⁰ says that the close connection of status dysraphicus with syringomyelia ought now to be generally realized. One can agree, he says, with those authors who wish to draw no line of demarcation between them. He regards it as "a matter of personal taste whether we will speak of a rudimentary lumbo-sacral syringomyelia or of a status dysraphicus (myelodysplasia)." The innumerable gradations pass insensibly from one to the other.

In 1928 De Vries¹⁶ reported a case of unilateral clubfoot in a Chinese at 30 years of age. The condition appeared following an injury and exhibited trophic disturbances and infection. Spina bifida was present as was also enuresis. The temperature sense was lost in both feet and, to a lesser degree, the pain sense, affecting chiefly the first and second sacral dermatomes. Pes cavus and trophic disturbances in both of the feet were present. De Vries called this a case of myelodysplasia (the term status dysraphicus had not yet found wide vogue). He points out that in extreme cases, in which glial proliferation is the main feature, the term lumbosacral syringomyelia may rightfully be used, but he believes that there are many transitional forms with slight neuroglia fiber production around the central canal in already existing congenitally deformed nervous tissue which do not fall into this category. He believes the term myelodysplasia (status dysraphicus) is applicable even when progressive symptoms do exist, provided they are largely of a trophic nature and do not give the typical progressive atrophies and sensory disturbances of syringomyelia.

Patients with status dysraphicus infrequently come to autopsy, so that not a great deal is known concerning the degree of pathologic involvement present. In the four patients whom Bremer autopsied, in whom there was clinical evidence of the condition, increase of glia tissue was found behind the central canal, which did not reach the posterior horns. One of these cases showed hydromyelia of the spinal cord. In this group the changes were for the most part confined to the cervical region.

None of our patients has come to autopsy, and we are unable to say to what degree the spinal cord is involved. We have been unable to follow our cases for a long period, but it would seem that the older members have shown the lack of progression which is so characteristic of true syringomyelia. The

deformities and loss of members seem to have followed complications brought about by infections. Two of the third generation appear to have more advanced neurological changes than those of the second generation, and the onset, according to the history, was at an earlier age. Lack of progression is our main clinical support for classifying these cases as status dysraphicus.

The similarity of the vasomotor and trophic disturbances that are such a prominent feature in many of these cases to those observed in Raynaud's disease naturally raises the question. Could they belong in the category of that syndrome? We have already pointed out that our attempts to precipitate these symptoms in one member of our group were not successful. Everything in Raynaud's disease points to a disorder of the vegetative nervous system and not of the central nervous system. The observations of many authors, however, show that the vasomotor disturbances which are sequels of nerve destruction can arouse symptoms very similar to those of Raynaud's disease. In such cases it is not difficult to demonstrate the destruction of the nerve as the cause of the phenomena. Cassirer⁴¹ has pointed out that the degenerative muscular atrophy so characteristic of syringomyelia is not observed in Raynaud's syndrome, and that the extent of gangrene is greater in the former. In addition, the fact that in Raynaud's disease the vasomotor phenomena come in definite attacks, which abate to be repeated, and that these attacks are accompanied by pain, is a basis for differential diagnosis, since in syringomyelia and in status dysraphicus there is hypesthesia or even anesthesia, and the vasomotor and trophic symptoms are maintained at a static level. Cagel⁴² thinks that Raynaud's gangrene can suggest syringomyelia only on superficial consideration, since the absence of muscular atrophy and the demonstrated sensibility disturbances with dissociated characteristics make a mistake hardly possible.

It was on such grounds as these that we felt safe in excluding Raynaud's disease from further consideration and found in status dysraphicus the complete explanation of all the symptoms exhibited by this series of subjects in our family group.

CONCLUSIONS

1. A family group is studied, embracing three generations, in which various individuals present degenerative constitutional signs, consisting of impaired circulation to the extremities, disturbance of sensation in the lower limbs and feet and, in a few members, similar disturbances of the hands.

2. Structural anomalies and so-called stigmata of degeneration were present in varying degree in nearly all the subjects examined.

3. The question is raised whether the condition afflicting this group represents a familial syringomyelia or should rather be regarded as the condition status dysraphicus.

4. The literature is reviewed and the nature of the two concepts examined.

5. Status dysraphicus is a thoroughly definite constitutional type, in which the developmental disturbance, consisting of a faulty closure of the

neural tube early in embryonic life, is readily transmitted to off-spring as a dominant characteristic

6 The presence of status dysraphicus is revealed by the association of a typical group of pathologic characters, prominent among which are deformities of the feet with trophic and vasomotor disturbances and a dissociation of sensation, especially of heat and pain, such as are found in this family

7 Syringomyelia, although producing similar disturbances, is regarded as being of a progressive type, owing to a gliosis of the spinal cord

8 Not the dysplasias themselves, but their common foundation, the status dysraphicus, is revealed by these various heredo-degenerative manifestations, the ensemble of which should be regarded as belonging to status dysraphicus

9 Status dysraphicus is related to syringomyelia quite closely, as a constitutional substratum for the latter, but is lacking in the progressive characters of genuine active syringomyelia

10 In view of this lack of progression and the relatively static nature of the defect that marks this family, it is concluded that the disturbances are owing to the presence of a well-marked constitutional status dysraphicus

11 The relation of status dysraphicus to other nervous diseases is still far from clear and requires further study

Grateful acknowledgment is extended to Dr Herbert Crockett, formerly Resident in Neuro-Surgery at the Los Angeles County General Hospital, for his kind cooperation and help in assisting with the records on one of the patients, to Dr Lee Rice of San Antonio, Texas, who very kindly examined and sent reports on one of the patients, to Dr Alfred Ackermann of Oklahoma City who helped with the translation of some of the literature and, finally, to many others including the patients themselves who have helped make this study possible

BIBLIOGRAPHY

- 1 SCHLESINGER, H Die Syringomyelie, Monograph, 2d ed, 1902, Deuticke, Leipzig
- 2 FERRANNINI, A Nucleo nosologico della siringomyelia definito da una sua forme familiare sinora non descritta, *Riforma med*, 1894, ii, 735
- 3 NALBANDOFF, S S *Vratch*, 1899, p 1399, Abstr, *Rev neurol*, 1900, viii, 417
- 4 PREOBJAJENSKI, P A Syringomyelie hereditaire, *Vratch*, 1900, p 120, Abstr, *Rev neurol*, 1900, viii, 984
- 5 KRAFFT-EBING, R Cited by Schlesinger¹
- 6 VERHOOGEN, R, and VANDERVELDE, P La syringomyelie, maladie familiale, *Soc Roy d sci med*, Bruxelles, *Ann dela*, 1894, iii, 267-300
- 7 BRUNS, L Familiare Syringomyelie im Lumbosakralmark, *Neurol Zentralbl*, 103, xxii, 599-602
- 8 FUCHS, A Ueber den klinischen Nachweis kongenitaler Defektbildungen in den unteren Rückenmarks-abschnitten (Myelodysplasie), *Wien med Wchnschr*, 1909, ix, 2142, 2262
- 9 MATTAUSCHEK, E Ueber Enuresis, *Wien med Wchnschr*, 1909, ix, 2154
- 10 CLARKE, J M, and GROVES, E W H Remarks on syringomyelia (sacro-lumbar type) occurring in a brother and a sister, *Brit Med Jr*, 1909, ii, 737-740
- 11 HAENEL, H Syringomyelie, in Lewandowsky's *Handbuch der Neurologie*, 1st ed, 1912, Pt. II, p 584
- 12 LUNDGAARD, CH Eigentümliche Veraenderungen im Rückenmarke eines Neugeborenen (kongenitale Syringomyelie), *Ztschr f d ges Neurol u Psychiat*, 1913, xx, 279-304
- 13 BIELSCHOWSKY, M, and UNGER, E Syringomyelie mit Teratom- und extramedullärer Blastombildung, *Jahrb f Psychiat u Neurol*, 1919-1920, xxv, 173-218

- 14 HENNEBERG, R, and KOCH, M Ruckenmarksbefunde bei Spina bifida, Monatschr f Psychiat u Neurol, 1920, xlvii, 1-33
- 15 BREMER, F W Klinische Untersuchungen zur Aetiologie der Syringomyelie, der Status dysraphicus, Deutsch Ztschr f Nervenheilk, 1926, xcvi, 103
- 16 DE VRIES, E Spina bifida occulta and myelodysplasia, with unilateral clubfoot beginning in adult life, Am Jr Med Sci, 1928, clxxv, 365-371
- 17 RILEY, H A Syringomyelia or myelodysplasia, Jr Nerv and Ment Dis, 1930, lxxii, 1-27
- 18 BREMER, F W Syringomyelie und Status dysraphicus, Fortschr d Neurol u Psychiat, 1937, ix, 103-113
- 19 CURTIUS, F, and LORENZ, I Ueber den Status dysraphicus Klinisch-erbblologische Untersuchungen an 35 Falle des Status dysraphicus und 17 der Syringomyelie, Ztschr f d ges Neurol u Psychiat, 1933, cxlix, 1-49
- 20 PASSOW, A Okulare Paresen im Symptombild des Status dysraphicus, Munchen med Wchnschr, 1934, xxxi, 1243-1249
- 21 COPPEZ, H Les symptomes oculaires du status dysraphicus, Jr belge de neurol et de psychiat, 1935, xxxv, 185-187
- 22 TOURAINE, M A Status dysraphicus, Bull Soc franç de dermat et syph, 1936, xliii, 444-446
- 23 BRAMANN Cited by Bruns
- 24 GOLDBLADT, H Syringomyelie bei Mutter und Tochter, Deutsch med Wchnschr, 1910, xxxiii, 1523
- 25 PRICE, G E Spinal gliosis occurring in three members of the same family, suggesting a familial type, Am Jr Med Sci, 1913, cxlvi, 386
- 26 KRUKOWSKI Zwei Falle von familiare Syringomyelie, Neurol Polsk, Warsawa, 1913, iii, 577, Abstr, Jahrb f Psychiat u Neurol, 1913, xvii, 738
- 27 KARPLUS, J F Syringomyelie bei Vater und Sohn, Med Klin, 1915, ii, 1344-1347
- 28 REDLICH, A Syringomyelie bei zwei Brudern, Wien med Wchnschr, 1916, iii, 1404
- 29 WEXBERG, E Zur Frage der konstitutionellen Disposition zur Syringomyelie, Ztschr f d ges Neurol u Psychiat, 1922, lxxix, 98-113
- 30 BARRE, J A, and REYS, L Syringomyelie chez le frere et la soeur, Rev neurol, 1924, xxxi, 521-530
- 31 KINO, F Ueber heredo-familiale Syringomyelie, Ztschr f d ges Neurol u Psychiat, 1926, 1927, cvii, 1-15
- 32 SCHULTZE, F Familiar auftretendes Malum perforans der Fusse (familiale lumbale Syringomyelie), Deutsch med Wchnschr, 1917, xliii, 545
- 33 KLIPPEL, M, and FEIL, A Syringomyelie et spina bifida combines, le syndromie hydro-myelique ependymaire et arachnoidien, Presse med, 1921, xxix, 971
- 34 GOEBBEL, R, and RUNGE, W Eine familiare Trophoneurose der unteren Extremitaten, Arch f Psychiat, 1917, vii, 297-364
- 35 WEITZ, W Beitrag zur Aetiologie der Syringomyelie, Ztschr f Nervenheilk, 1924, xxxii, 57
- 36 STAHL, E Ueber Remissionen im Symptomenbild der Syringomyelie, Deutsch Ztschr f Nervenheilk, 1915, liii, 404-422
- 37 VAN EPPS, C, and KERR, H D Familial lumbosacral syringomyelia, Jr Iowa State Med Soc, 1937, xxvii, 633-636
- 38 BARRAQUER, L, and DE GISPERT, I Die Syringomyelie, eine familiare und hereditare Krankheit, Deutsch Ztschr f Nervenheilk, 1936, cxli, 146-152
- 39 SMITH, E M Familial neurotrophic osseous atrophy, Jr Am Med Assoc, 1934, cii, 539-595
- 40 CURTIUS, F Die Erbkrankheiten des Nervensystems, 1935, F Enke, Stuttgart
- 41 CASSIRER, R Vasomotorisch-trophische Erkrankungen, in Bumke and Foerster's Handbuch d Neurol, 1935, xvi, 319-393, Julius Springer, Berlin
- 42 CAGFL, O Syringomyelie, in Bumke and Foerster's Handbuch d Neurol, 1935, xvi, 319-393, Julius Springer, Berlin

EOSINOPHILIA AND PNEUMONITIS IN CHRONIC BRUCELLOSIS; A REPORT OF TWO CASES¹

By KENDALL A. ELSON, M.D., and FRANZ J. INGELFINGER, M.D.†,
Philadelphia, Pennsylvania

THE co-existence of extensive pneumonic infiltration, eosinophilia and immune reaction to *Brucella abortus* has been recently observed by us in two patients. The striking similarity of the clinical picture in these two cases suggests that the association of phenomena was not purely fortuitous, but that a common etiology exists. The syndrome was unfamiliar to us, and, so far as we can determine, has not hitherto been described. We believe it to be a manifestation of brucellosis, but only the recognition and study of similar cases will substantiate this assumption.

CASE REPORTS

Case 1 S. K. L., a 29-year-old housewife, first developed a fever of 99°–100° F in 1934. It recurred intermittently until her admission to the gastrointestinal outpatient clinic of this hospital in February 1935. Physical examination was then essentially negative. Roentgen examination of the lungs was negative. Routine and differential blood counts were negative. After an afebrile period the fever recurred in March 1935 and intermittently throughout the following summer. Her general health was poor, she was underweight, and had a variety of ill-defined gastrointestinal complaints considered to be of nervous origin. During 1937 and 1938 she had five attacks of cystitis which subsided, as a rule, within a week. Urine cultures disclosed no organisms of significance. In December 1938 elevation of temperature to 102° F in the evening occurred. She developed chills, malaise, a slight unproductive cough and marked tachypnea. She was admitted as a bed patient on December 16, 1938 (figure 1).

On physical examination the temperature was 101° F, pulse 112, respirations 36. She was dyspneic and slightly cyanosed but not seriously ill. The physical signs over the chest were few. Occasional râles were heard at both apices. The breath sounds were increased in intensity over the interscapular areas, but nowhere were signs of consolidation elicited. Examination of the heart was negative. The abdomen was slightly distended, and generalized tenderness was present. The physical examination was otherwise negative.

Roentgen examination of the chest (figure 2) showed extensive multiple bilateral exudative lesions extending to the peripheral pleura. The diagnosis was uncertain. The appearance of the shadows suggested atypical bronchopneumonia or a mycotic lesion rather than tuberculosis.

Blood examination disclosed a moderate anemia, leukocytosis of 16,600 and eosinophilia of 27 per cent. Blood, urine and sputum cultures were negative. Repeated stool examinations failed to reveal ova or parasites. A tuberculin test (01 mg) was negative.

Within two weeks distinct clinical improvement had occurred, although the temperature rose to 99° or 100° F every evening and the eosinophilia increased to 40 per

* Received for publication December 29, 1939.

From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania.

† Fellow in Gastro-Enterology.

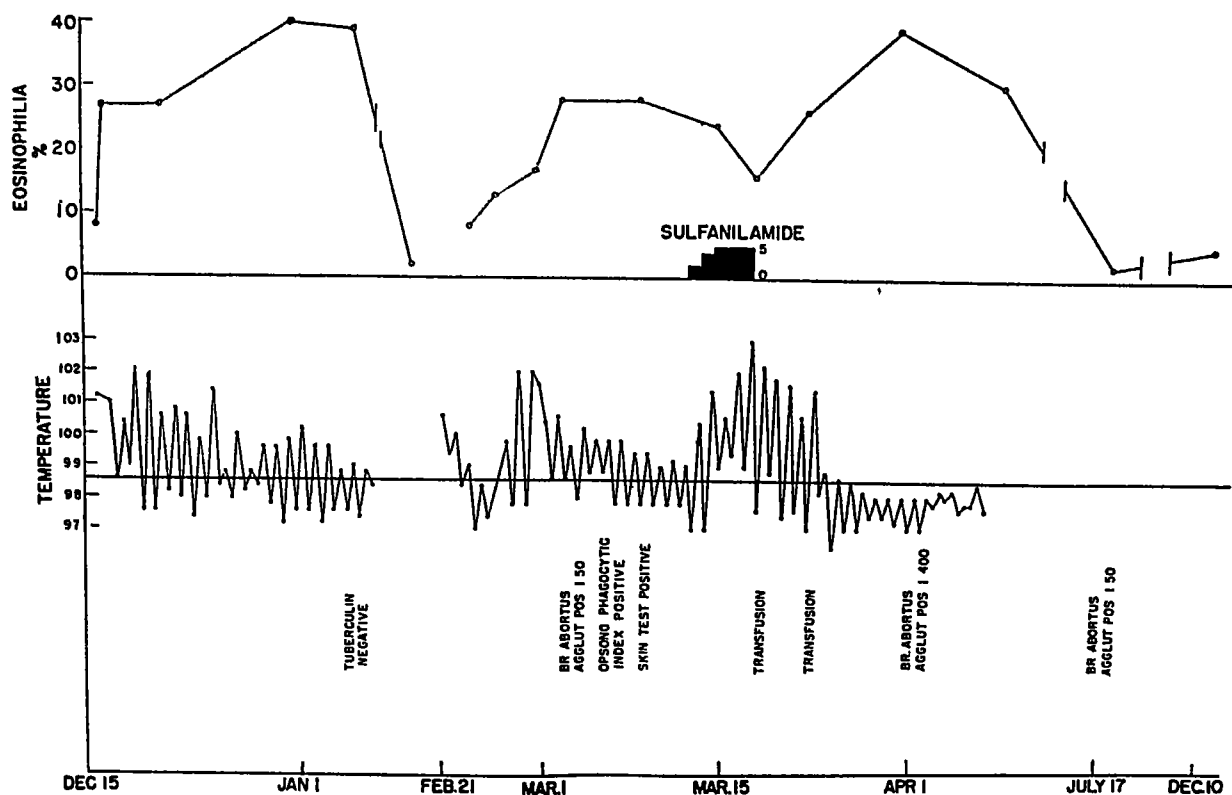


FIG 1 Case 1 The temperature, the percentage of eosinophiles and the results of immunologic tests during and after the height of the disease

cent Examination of the chest was essentially negative and the roentgen appearance of the lungs was correspondingly improved. She was discharged from the hospital on January 6, 1939. By January 26 the lesions in the lungs were not visible in roentgenograms except in the left upper lobe. The leukocyte count was 10,500 of which only 2 per cent were eosinophiles.

In spite of the subsidence of the pneumonitis and eosinophilia she continued to have fever almost daily. By the second week in February it was apparent that the pneumonic process had recurred. Generalized râles and harshness of the breath sounds were again heard over the chest and the temperature reached 101° to 102° F at night. She was, therefore, re-admitted to the hospital on February 21, 1939. Physical signs were essentially those of the first admission. Leukocytosis of 10,000 was found, and the eosinophile count rose within a week from 8 to 28 per cent. Serum gave a positive agglutination for *Brucella abortus* in a dilution of 1:50. In determining the opsonophagocytic index, 25 polymorphonuclear cells were examined, 18 showed moderate to marked phagocytosis of *Brucella abortus*, four contained a few organisms, and only three contained none. A skin test with Brucellergin was strongly positive. Attempts to culture the organism from blood, stools and urine were unsuccessful.

Sulfanilamide, 2 to 5 grams daily, was administered for five days. An explosive exacerbation in the pneumonitis occurred, râles were heard throughout the chest, the temperature rose to 103° F, dyspnea became intense, and the clinical condition was grave. The drug was discontinued and after oxygen therapy and repeated transfusions improvement occurred. Within two weeks after administration of the drug the temperature was normal and remained so for the duration of the illness. The evidence of pneumonitis disappeared both clinically and radiologically. After subsidence of the fever the *Brucella abortus* agglutination was positive in a dilution of 1:400. The eosinophilia persisted after recovery was otherwise complete. In July,



Fig 2 Case 1 Roentgenograms of the chest taken (A) on December 17, 1938, and (B) July 17, 1939

1939, three months after discharge, the leukocyte count was 8,700 with 2 per cent of eosinophiles. On both physical and roentgen examination the chest was entirely normal (figure 2). The *Brucella abortus* agglutination was positive in a titre of 1:50. At the present (December 1939) recovery is apparently complete.

Case 2. Mrs. C. S., a 58-year-old Polish woman, was admitted to the medical wards of the University of Pennsylvania Hospital on December 2, 1938. She had developed chills, fever and a cough in June, 1938. She was then confined to bed for only two days, but had noticed dyspnea and a persistent productive cough for the remainder of the summer. In October 1938, she developed paresthesia in the right arm and hand, and to a lesser degree in the left arm. Pain was present in the right hand, arm, and right chest, especially on exposure to cold. She had lost 18 pounds (16 per cent of body weight) in the eight months prior to admission. Her appetite was poor. Repeated epistaxis had occurred in the month preceding hospitalization. For the preceding three and a half years she had lived on a farm and had consumed raw milk from uninspected cattle. Pork and beef from freshly killed animals had been ingested. The remainder of the history was negative.

Physical examination revealed an emaciated middle-aged woman with normal temperature, pulse and respiration. Blood pressure was 138 mm Hg systolic and 74 mm diastolic. She had a non-productive cough. The skin was dry and inelastic. The muscles were generally wasted, but those of the right shoulder girdle and right arm were more atrophied than on the left side. Only a few teeth remained. The tongue was smooth and its edges were abnormally red. The tonsils were inflamed. Expansion of the chest was poor. Râles were heard over both lungs, but chiefly on the left side. Breath sounds were generally accentuated. The percussion note was not impaired. The heart was slightly enlarged on percussion. The abdomen was normal. Vibratory sense in the legs and feet was impaired, but tendon reflexes were preserved. A moderate grade of generalized arteriosclerosis was found.

Roentgenographic examination of the chest (figure 3) revealed moderate cardiac enlargement and marked increase in the hilar shadows. Multiple irregular lesions throughout both lung fields suggested a chronic inflammatory interstitial pneumonitis. The right costophrenic sulcus was obliterated.

Examination of the blood disclosed a marked eosinophilia. The leukocytes varied in number from 9,800 to 15,000, of which 29 to 42 per cent were eosinophiles. The other formed elements of the blood were normal. Other members of the family did not have eosinophilia. *Brucella abortus* agglutinins were strongly positive in the blood in a titre of 1:100, weakly positive in 1:200 dilution. A later test was strongly positive in a dilution of 1:200. Agglutinins for the typhoid-paratyphoid group were negative. Repeated sputum examinations and culture for tubercle bacilli were negative. Sputum culture yielded an abundant growth of a Friedlander-like organism not known to be pathogenic. Stools were repeatedly examined for ova and parasites with negative results. Skin tests to a variety of foods and to trichina antigen were negative. The fasting blood sugar was normal, but the sugar tolerance curve was of the diabetic type.

During hospitalization the pain in the right arm and hand, which constituted the chief complaint, was quickly controlled by analgesics and by application of heat. Temperature varied between 97° and 100.4° F. In spite of a high caloric, high vitamin diet the appetite remained poor, and weight loss of four pounds occurred in three weeks. The cough persisted, and the physical signs over the chest were essentially unchanged. She was discharged at her own request on December 23, 1938.

In March 1939, the patient was readmitted for further observation. In the interim she had lost five and a half pounds and had continued to cough. Pain in the right arm and hand was still present. Physical examination disclosed no new abnormalities. Eosinophilia of from 20 to 26 per cent was again observed. Leukocytes

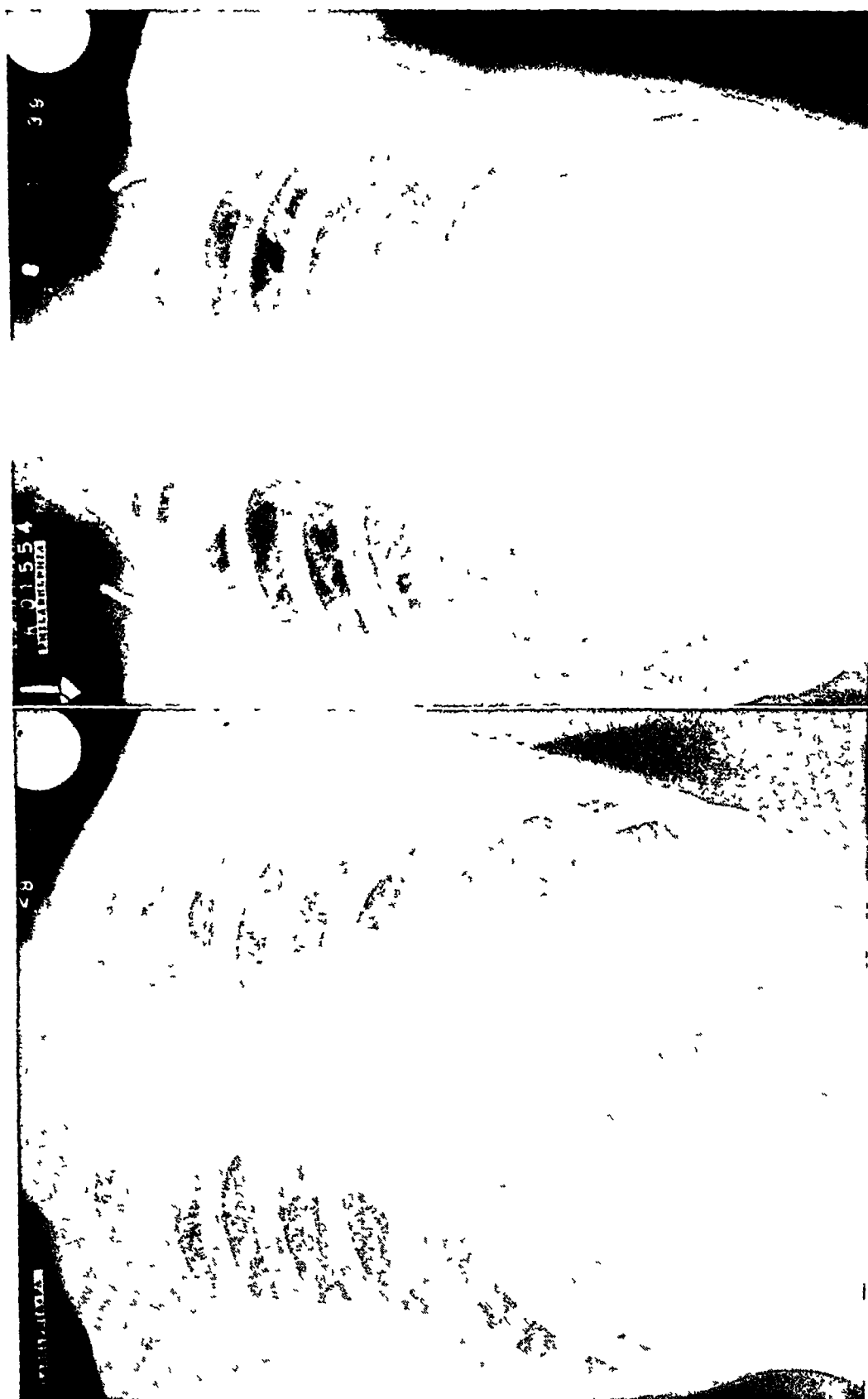


FIG 3 Case 2 Roentgenograms of the chest taken (A) on March 28, 1939, and (B) August 1, 1939

varied in number from 8,200 to 13,200. The opsonophagocytic test revealed that of 25 polymorphonuclear cells observed 18 showed marked and seven showed moderate phagocytosis of *Brucella abortus*. A skin test with Brucellergin was positive. Chest roentgenogram again showed pneumonitis. She was given palliative treatment and discharged on April 1. In the ensuing six months she gained 14 pounds, and became largely free of symptoms except for occasional cough. The leukocytosis and eosinophilia disappeared. In August, 1939 the *Brucella abortus* agglutination was positive in a titre of 1:800. The pulmonary signs observed by roentgen-ray had regressed (figure 3), and physical examination of the chest was negative.

DISCUSSION

Both of these patients had diffuse pulmonary infiltration, fever, eosinophilia, and an immunologic reaction to *Brucella abortus*. In attempting to establish a common etiology the diagnosis of brucellosis deserves first consideration. The agglutination titre, while initially low, later rose to levels generally accepted as significant. The positive skin test and opsonophagocytic index added further evidence of immune response to *Brucella abortus*. These positive tests may merely indicate past infection rather than active brucellosis. However, lacking a typical clinical picture, the diagnosis usually rests on immunologic evidence alone, since culture of the organisms is uncommon. In case 1 the history of long standing recurrent fever is in harmony with a diagnosis of chronic brucellosis, although no known exposure to the organism had occurred, in case 2 exposure to infection seemed likely.

If the assumption is correct that the disease process was caused by infection by *Brucella abortus*, then the syndrome of fever, pulmonary infiltration and eosinophilia must be regarded as an unusual manifestation of brucellosis. Pulmonary abnormalities without eosinophilia have frequently been reported^{1, 2, 3, 4} and may constitute the outstanding clinical feature of the disease. In many of the described cases, as in our own, the roentgenologic evidence of pulmonary disease was more striking than were the physical signs. Increase in the bronchovascular markings, marked hilar infiltration, and diffuse bronchopneumonic consolidation often resulting in extensive fibrosis have been frequently described. The lesions may simulate those of tuberculosis. Pulmonary abscess, pleural thickening and pleural effusions have occurred.

Eosinophilia, on the other hand, is not a usual observation in undulant fever. In several large series^{5, 6, 7} it was not observed. Calder, Steen and Baker⁸ observed eosinophilia of 5 per cent or over in one-fifth of their patients, but this is exceptional.

It is of interest to consider whether our cases are related to those of transient pulmonary infiltration and eosinophilia first described by Loeffler⁹ in 1931. This syndrome, subsequently reported by a number of authors in Europe,^{10, 11, 12, 13} is characterized by transitory and rapidly shifting infiltration of the lungs which usually disappears within three to eight days after a very benign clinical course with minimal symptoms and objective signs.

Eosinophilia usually ranges between 15 and 35 per cent but has exceeded 60 per cent in some instances. A marked seasonal incidence was observed by Loeffler, most of the cases occurring during the summer months. Although the exact etiology of the syndrome is in doubt, many of the cases were tuberculous. Most authors ascribe the lesion to an allergic or "hyperergic" response of pulmonary tissue to a generalized infection, although Wild and Loertscher¹⁴ attributed it to migration of ascaris larvae through the lungs, and Engel¹⁵ points to the similar clinical picture seen in China, thought to be due to sensitivity to privet. Agglutination tests for the brucella group were not reported in the cases referred to above, and it is impossible, therefore, to determine whether or not these organisms are concerned in the etiology of Loeffler's syndrome. Our cases differed from his in two main respects: the pulmonary lesion was by no means clinically insignificant, nor was it transitory in nature. Neither had any obvious evidence of allergy or of tuberculosis.

A final heterogeneous group of diseases is occasionally characterized by pneumonic infiltration and eosinophilia. Dobreff and Toscheff¹⁶ have described eosinophilia of 30 to 59 per cent in a patient recovering from acute bronchopneumonia, and Gsell⁹ states that 5 per cent of all patients recovering from acute pulmonary infection have eosinophilia of 10 per cent or over. Hodgkin's disease and periarteritis nodosa are known to produce bizarre clinical pictures having certain features in common with our cases. The apparent recovery of our patients tends to rule out these diagnostic possibilities. Minot and Rackemann¹⁷ studied the incidence of respiratory abnormalities in trichinosis and report a number of instances in which the most significant initial features of the disease were pulmonary in origin. In our Case 2 negative skin tests with trichina antigen and a negative muscle biopsy were obtained. In Case 1 tests were not made, since pork was rarely included in the dietary.

Although the usual causes of eosinophilia have been excluded in our cases, we are cognizant of the fact that the evidences of allergy often escape detection. Whether a local tissue sensitivity to *Brucella abortus* or its products existed and ultimately resulted in an allergic or "hyperergic" pulmonary reaction remains a matter of speculation.

SUMMARY

Two patients are described who presented a conspicuously similar clinical picture consisting of fever, pneumonitis, eosinophilia and immune response to *Brucella abortus*. Both made a good recovery. The disease process is regarded as a manifestation of chronic brucellosis. Although this etiologic possibility deserves first consideration, the exact cause of the syndrome remains undetermined.

BIBLIOGRAPHY

- 1 BOGART, F B Pulmonary changes in undulant fever, *South Med Jr*, 1936, xxix, 1
- 2 LAFFERTY, R H, and PHILLIPS, C C Pulmonary changes in patients suffering from Malta fever, *South Med Jr*, 1937, xxx, 595
- 3 JOHNSON, R M Pneumonia in undulant fever—a report of three cases, *Am Jr Med Sci*, 1935, clxxxix, 483
- 4 BEATTY, O A Manifestations of undulant fever in the respiratory tract, *Am Rev Tuberc*, 1937, xxxvi, 283
- 5 MUNGER, M, and HUDDLESON, I F A preliminary report of the blood picture in brucellosis, *Jr Lab and Clin Med*, 1939, xxiv, 617
- 6 ANGLE, F E Treatment of acute and chronic brucellosis, *Jr Am Med Assoc*, 1935, cv, 939
- 7 SCHMID, N Blut und Knochenmark bei Morbus Bang, *Schweiz med Wchnschr*, 1939, xx (NS), 191
- 8 CALDER, R M, STEEN, C, and BAKER, L Blood studies in brucellosis, *Jr Am Med Assoc*, 1939, cxii, 1893
- 9 LOEFFLER, W Die fluechtigen Lungeninfiltrate mit Eosinophilie, *Schweiz med Wchnschr*, 1936 xvii (NS), 1069
- 10 LEITNER, S J Hyperergische, fluechtige, mit Eosinophilie einhergehende Infiltrate der Lungen bei Tuberkulose und Abortivpneumonien, *Acta med Scand*, 1938, xcvi, 473
- 11 MEYER, H E Zur Kenntnis fluechtiger, mit Eosinophilie im Blut einhergehender Lungeninfiltrate, *Med Welt*, 1937, xi (2) 1808
- 12 GRAVESEN, P B Transitory lung infiltrations with eosinophilia, *Acta med Scand*, 1938, xcvi, 523
- 13 STAHEL, K Sternalbefunde bei eosinophilem Lungeninfiltrat, *Folia haemat*, 1938, lix, 341
- 14 WILD, O, and LOERTSCHER, M Zur Aetologie der fluechtigen Lungen-Infiltrierungen, *Schweiz med Wchnschr*, 1934, xv (NS), 829
- 15 ENGEL, D Zur Frage des anaphylaktischen Fruehjahrsoedems der Lunge, *Beitr z Klin d Tuberk*, 1937, lxxxix, 323
- 16 DOBREFF, M, and TOSCHEFF, A Ueber einen Fall von spontan auftretender kryptogenetischer lang dauernder exzessiver Bluteosinophilie, *Deutsch Arch f klin Med*, 1935, clxxviii, 230
- 17 MINOT, G R, and RACKEMANN, F M Respiratory signs and symptoms in trichinosis, *Am Jr Med Sci*, 1915, cl, 571

WHITHER?

By JAMES ALEXANDER MILLER, F A C P , *New York, N Y*

THE question which I have posed as the subject of my address this evening is on the lips or in the hearts of millions of the population of the world today

It is obvious that I can have no intention of addressing myself to that vast audience. It is rather my purpose to suggest a searching of hearts and minds to our profession here in America and particularly to that portion of it which is represented in the Fellowship of the American College of Physicians. It was my thought that this Annual Convocation is especially timely for such introspection, inasmuch as upon this occasion a considerable body of young men are for the first time inducted into the privileges and responsibilities of Fellowship in the College.

If we are fruitfully to project our thoughts along a future path, it would seem wise first to indicate the point of departure. Where are we today?

Time allows for only a few observations.

We are in the full tide of a period of progress in knowledge, in science, and in medicine, such as history has never before known. American medicine is in the fore-front of this progress, and it is the great privilege of our generation to be participants in it.

Physicians engaged in research, in laboratory and clinic are constantly adding to our new knowledge. Practitioners are eagerly engaged in the exciting effort to put this knowledge into practical application.

More than elsewhere in the world, here in America the necessary tools are placed in our hands, in hospitals, in clinics, in laboratories, in equipment.

Educational opportunities for student and practitioner have never been greater, and you younger men are equipped in a manner unthought of by previous generations. Not only in diagnosis and treatment, but also in the prevention of disease, there have been great achievements, so that many dread scourges of the past are gone forever, and the fascinating prospect of the conquest of new similar worlds is ever before us.

These are a few of the bright lights on one side of the shield. What are some of the shadows to be detected upon the reverse?

Although the medical profession is giving a service of a higher quality than ever before, although the general health of our country measured in terms of general morbidity and mortality has been progressively improved, yet, there has probably never been a time when the medical profession has been under more widespread criticism. This anomalous situation is disheartening, and a constant source of wonder to us.

It may be worth our while to stop a moment and attempt to analyze it.

* Convocational Oration, American College of Physicians, Twenty-fifth Annual Session, Boston, Mass., April 23, 1941

It is my impression that in spite of the inevitable development of specialism, which has modified the intimate personal relationship between physician and patient of former days that, individually, the warm feeling of understanding and affection for physicians as personal and family friends still persists

It would appear that it is public feeling toward the profession as a whole which has changed

In common with all other groups, we have become organized. Organizations are essentially impersonal. In some unfortunate manner, our organization has been manoeuvred into a defensive position. It is consequently felt that our virtues and our services of which we have always been subconsciously proud, something to be taken for granted, must now be vocalized.

Security, which nowadays appears to be more desirable than adventure, has become our important concern, to be militantly defended. We physicians, who have been notoriously complacent in such matters, being so very busy with our immediate tasks, are now thrown into the midst of the modern economic maelstrom.

The character of the services we render is in danger of being overlooked in the discussions over their compensation. Being individualists and conservative by nature and by training, more accustomed to quietly exercise our privileges for the benefit of others than to fight for our own rights, we are confused.

We frankly don't like it. Yet the rent must be paid, and that is not always easy.

A not unimportant factor in this situation is the more general diffusion of knowledge, or, at least, information, concerning matters medical. We physicians ourselves have fostered this change. Some of us can remember when the physician was a sort of high priest of mystery whose dogmatic pronouncements were delivered without explanation, to be accepted without question. This, to some extent, may have been faith healing, but to us now it smacks of quackery.

Intelligent cooperation is now the accepted basis of the relationship between physician and patient. Thus, to the other available sources of information, the physician adds his bit to the education of the laity in matters of health and disease. But this engenders among our patients a feeling of the right to criticize as well as to gratefully accept, and thus may the unwary physician be hoist by his own petard.

The press, the radio, and the medical advertiser carry the message still further and finally it reaches that guardian of a democratic people, the politician. Thus we are confronted with the greatest of modern bugaboos, State medicine. By this time, to be sure, enthusiasm may have outrun the truth but the alleged basis is, nevertheless, some sort of medical knowledge.

And why not? In these days, when the mid-Victorian veil is withdrawn from all secrets, whether personal or business, and the government, becom-

ing increasingly paternalistic in its concern for all of its people, reaches out into all other spheres of activity, why should medicine escape?

The answer is that it cannot, and probably should not, and the proper response from us should then be an intelligently insistent, "How?", rather than an indignant, "Why?"

Probably one of the most justifiable bases for criticism of present practice is the comparative neglect of social and preventive medicine

In discussing "Trends of Medical Education" recently, Sigerist says "We still need, more than ever, a scientific physician, well trained in laboratory and clinic. But we need more, a social physician who, conscious of developments, conscious of the social functions of medicine, considers himself in the service of society

"The barriers between preventive and curative medicine must be broken down. This cannot be achieved by adding a few courses to the curriculum. A new attitude must be developed. The student must become interested in health, not only in disease. Clinical medicine must be taught differently from heretofore. Every case must be analyzed medically and socially as to the factors that have made it possible, and conclusions must be drawn as to how to prevent similar cases in the future."

I think that we must concede that these words paint a fairly accurate picture of the present, and are a challenge to the future.

It also must be recognized that prominent among the social considerations are the surrounding economic conditions, and that in the search for security, recognition of these social and community problems is essential to an understanding of our present situation, and that toward that end greater emphasis upon the prevention and social aspects of medicine appears indicated.

I have thus far endeavored to sketch a few of the important factors which influence medical practice in America today. With this background, I approach the main theme of my address.

In other words, where do we go from here?

In these confused times, no one could have the temerity to attempt a categorical answer to this far-reaching question. It is my purpose simply to consider certain angles of the problem as they apply particularly to medical men as suggestions for thought, rather than for a definite program of action.

John Buchan has recently expressed something of what is in my mind.

"We are condemned to fumble in these times, for the mist is too thick to see far down the road. But in all our uncertainty, we can have Cromwell's hope, 'To be a Seeker is to be of the best sect next to a Finder, and such an one shall every faithful Seeker be at the end.'"

This is particularly true for medicine, the constant eager zest for new knowledge. For those of us now well beyond undergraduate student days, we call it, *Continuing Education*.

This is no new idea to this College. It is in fact the foundation of its policies, the essence of its program, the very reason for its existence. Why then bother to emphasize so self-evident a fact? It is because it may be so taken for granted that in the midst of the present changing order and confusion of ideas, we may fail to hold to the realization that continued learning is the fundamental basis for progress in our profession.

Some of us who are older can look back and trace the subsequent careers of many who started with equal opportunities. Analyzing the outstanding characteristics of those who have achieved professional success, the capacity for sustained work and productive study appears paramount. When a practitioner ceases to be a student, his quality begins to shrivel and finally to die.

To those of you who are younger, the opportunities today are greater than ever before and the College offers many of them. Your election to fellowship is not a decoration for accomplishment, but rather a recognition of your potential capacity for achievement. It is a challenge, not a reward.

Recent developments in the National Defense Program, with the not unlikely possibilities of actual War, have materially affected the outlook of the medical profession. We may well ask what effect they will have upon our plans for continuing medical education.

In common with the rest of the country, we as physicians must and will meet our obligations which will involve many sacrifices, but the world situation demands that on no account should we allow ourselves to be diverted from our fundamental responsibility to maintain, even more than ever, a high quality of medical science.

In Europe, to which we owe so much of our background in culture and in science, the foundations of the old order are being ominously shaken. Universities are disrupted, libraries are being destroyed, orderly scientific research is at a standstill.

Together with all other social forces, medical science and medical research are being diverted solely toward the desperate problem of war and of defense. They are in a death grapple for existence with no possible constructive program for the future. In this country alone are orderly progress and independent scientific investigation possible. At no time in the world's history has a nation been so urgently called upon to keep aloft the torch of freedom and of science and in no field of endeavor is this demand more insistent than in medicine.

The President of the United States has said that America should be the arsenal for the Democracies. For us it must be more than that. America must also be the citadel of free and independent scientific thought if the present is to be saved and the future assured. This College is one of the important bastions of that citadel.

The present crisis may well tend to make continuing medical education more difficult, but actually it renders it even more essential. Disappointments may await us, both individually and collectively, but they can be overcome by

hard persistent effort, which they should enhance rather than discourage. We cannot, *must* not fail to meet this challenge.

At the close of a memorable address, a number of years ago, one of the greatest and most beloved leaders in American medicine, Dr. Edward Livingston Trudeau, left us this ringing message, which has even more meaning today than it had then:

"Let us not, therefore," he said, "quench the faith, nor turn from the vision, which, whether we own it or not, we carry, as Stevenson's lantern-bearers their lanterns, hidden from the outer world, and thus inspired, many will reach the goal. And if for most of us, our achievements must inevitably fall short of our ideals, if, when age and infirmity overtake us, 'we come not within sight of the castle of our dreams, nevertheless, all will be well with us.' For, as Stevenson tells us rightly, 'to travel hopefully is better than to arrive, and the true success is in labor.'"

In addition to continuing education to develop our knowledge, I would suggest that, in order to successfully meet the changing conditions which lie before us, we need the development of our powers of *adaptation*.

Trained in science we physicians are familiar with this term as a biological concept. Steeped in tradition, however, we have been slow to adopt it as an essential rule of conduct. We are conservatively skeptical of radical change, for we appreciate its dangers. Are we not in equal danger of failing to meet the challenge of changes which are already upon us and which we cannot ignore?

Our cloistered existence, which keeps us enveloped in the effort to attain knowledge and to put this knowledge into practical application, is outmoded and we must widen our horizon to include the larger field of social and community responsibility.

We cannot yet see clearly just what form it will take, but it is certain that the practice of medicine of tomorrow will be quite different from that of today or of yesterday.

The penetrating mind of Dr. George Vincent recognized this fact fifteen years ago.

In a brilliant address entitled "The Doctor and the Changing Order," he thus expressed himself,

"'The old order changeth.' That is a law of life. To this changing order all, even doctors, must adapt themselves."

"This adaptation takes place, not through large comprehensive, elaborate schemes of reform but piecemeal, here and there, now and then, by happy chance, by trial and error, opportunistically, unconsciously."

"The larger the number of minds that see the trend of things the better the chances of gradual adjustment. So studies, comparisons of experience, experiments, demonstrations, discussion, all play a part and are welcomed."

"To sum up. It looks as if society means to insist upon a more efficient organization of medical service for all groups of people, upon distribution

of the costs of sickness over large numbers of families and individuals, and upon making prevention of disease a controlling purpose ”

“Just how these ends will be gained only a very wise or a very foolish man would venture to predict One thing seems fairly certain, in the end society will have its way ”

This is a message from the past to which we may well still give heed today It is to be noted how closely Dr Vincent's ideas of fifteen years ago parallel those of Prof Sigerist of today These are not isolated expressions of opinion, but represent contemporary thought indicating definite trends of the times We cannot ignore them We must adapt ourselves to them

It would appear from our discussion thus far, that the main challenge to our profession lies in the social and community problems which confront us

I am reluctant to allow it to finish upon that note

The character and influence of any group is the sum total of that possessed by the individuals which compose it Faulty organization may hamper the possibilities for individual expression, but, by and large, no group can rise above the level of its individual components

This brings us back again to individualism as a fundamental factor, and in this field we physicians are supposed to be shining examples My point is that we, as individuals, must share in the responsibility of our profession as a whole I am not at all sure that the criticisms that have been leveled at our profession, as a group, may not have some basis in a subtle change which has come over the attitude of many of us as individuals

We hear much of such watchwords of modern social progress as security, rights, privileges We hear all too little of that more fundamental requirement, obligation Whatever excuse may be offered for this situation in other walks of life, it is not justified for a profession such as ours, which is dedicated primarily to the service of others

There is certainly no such situation in the American College of Physicians For a number of years it has been my privilege to be closely identified with this College, and during that time it has been one of my main professional interests I know intimately not only your leaders, but also hundreds of our individual members, and I know that you are fired by high ideals and faithful to them in practice Altogether, you constitute a grand group of men measured by any standard

The present situation cries out for aggressive leadership Where may we look for it with greater confidence than among the members of our own College?

As a College, we have very wisely, I think, adopted the policy of taking no active part in the sphere of social and economic medicine But as individuals we are also members of the general medical profession, and it is to you as individuals that I am now addressing myself.

What constitutes leadership?

It is interesting and significant that General Wavell tells us that General

Allenby, who was his preceptor in the art of war, placed character as the outstanding qualification for a military leader. And General Wavell himself, in a recent interview, also places the possession of character at the very head of the requirements essential for a successful commander.

If this be true for leadership in war, one of whose main objects is the destruction of life, how much more should it be so for medicine, which is dedicated to its preservation.

I shall not attempt to define character, but we all recognize it implies moral and spiritual qualities, as well as intellectual capacity. It is also essentially an individual attribute.

This brings us back to the thesis that if we are to provide leadership, we must conserve and develop individual character.

The present confusion in the world is more than a clash of arms or a conflict of interests. It is a fight to the death for basic principles. We need to preserve not only our "way of life," a phrase which to me connotes too much of physical comfort and complacency, but still more, we need to preserve the intellectual freedom and spiritual values in life which have been achieved through centuries of conflict and which we have inherited from those who have gone before us.

This cannot be accomplished by waging successful war, but rather by developing that inward strength, our character. Indeed, failing to do this, we may well win the war and lose the peace.

Now, this development of character and the achievement of leadership cannot be achieved by letting each day take care of itself, with no thought of the morrow. It is no haphazard endeavor. It involves constant and conscious effort.

We are going through times and experiences which try men's souls. The problems and difficulties which confront us, as a profession, are overshadowed by the world crisis in which we, too, are involved. In the end it will be the moral and spiritual qualities which will decide the issue.

Here we are, favored members of the world's leading nation and of a profession which appears capable of achieving more than ever before in our history. Yet, we are confused, uncertain, frequently disappointed, and consequently often depressed. In times such as these it is easy to drift from our moorings and to lose sight of our customary guiding beacons.

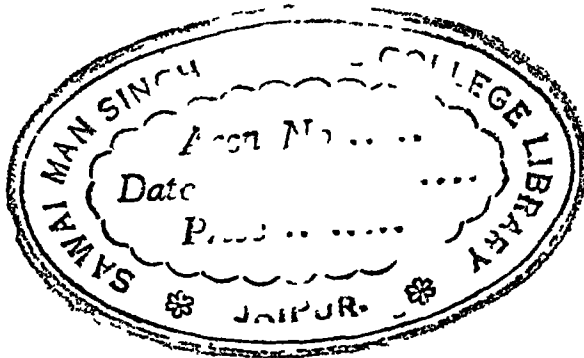
We ask for leaders to rescue us from our difficulties. With our background and potentialities, should we not rather be preparing to lead both ourselves and others?

To do this we must be freed from the entanglements of our daily routine and take time to think of basic principles. We need to reorientate ourselves frequently.

How would it be if we, as a strong cohesive group of physicians, could make an earnest conscious effort to perfect our own characters in order to meet our present great responsibilities, both as physicians and as citizens?

How would it be if, in order to do that, we could make it a practice from time to time to withdraw from our busy engrossing lives, from the anxiety and the confusion about us, into the quiet of our secret inner selves and there each of us, with whatever spiritual assistance our particular philosophy provides, call it God or by any other name, regularly attempt to chart the course that we are following?

There, at intervals, quietly and alone, let us each one of himself, earnestly ask the solemn question, WHITHER?



CASE REPORTS

MASKED HYPERTHYROIDISM AS A CAUSE OF HEART DISEASE (With Report of a Case With Long Standing Auricular Fibrillation Cured by Subtotal Thyroidectomy)*

By SAMUEL H. AVERBUCK, M.D., F.A.C.P., *New York, N. Y.*

ALTHOUGH masked hyperthyroidism as a cause of clinical heart disease has received well deserved emphasis by some authors (Lahey,¹ Levine,² Sturgis and Levine³) this subject has not received the adequate attention of internists. The thyroid factor, overshadowed by the signs and symptoms of heart failure, is extremely difficult to recognize, particularly in older individuals. In this older group of patients a diagnosis of the relatively more common arteriosclerotic coronary artery disease offers a ready explanatory etiology for the cardiac insufficiency. Its acceptance, however, automatically limits the therapeutic possibilities. In sharp contrast on the other hand is the opportunity for achieving a rapid and almost complete cure if thyroid hyperactivity can be identified as playing an important rôle in the cardiac breakdown. Although generally known to occur, there are few recorded examples of the miraculous transformation from chronically bed-ridden states of cardiac failure to comparatively normal health after subtotal thyroidectomy in this type of cardiac disease.

This presentation is offered as an example of how successful even long delayed subtotal thyroidectomy can be, illustrated by spontaneous resumption of normal sinus rhythm after operation in a patient who had had uninterrupted auricular fibrillation for four years. Furthermore, this case may serve as a text whereby the inherent diagnostic difficulties in this condition can be pointed out and the entire clinical picture reviewed.

CASE REPORT

W. M., a 65-year-old furniture salesman, came under observation in August 1938, complaining of weight loss. In the year past he had lost 20 pounds, with a total loss in four years of 40 pounds. Four years before, the patient had experienced attacks of paroxysmal tachycardia, but examination had revealed no cardiac abnormalities. Three and a half years previously his heart rhythm had become permanently irregular and a clinical diagnosis of auricular fibrillation had been confirmed by an electrocardiogram (figure 1A). His heart had continued to beat irregularly up to the present and he used digitalis sporadically. There was no dyspnea or palpitation except upon rather severe exertion, such as walking up grade or up steps. His appetite varied, but he was of the impression that his weight loss could not be explained by reduced food intake. There was a daily bowel movement but never diarrhea. He slept well and he could not recall excessive thirst, sweating, weakness, nervousness or excitability.

Thirty-two years previously a routine blood Wassermann test during an insurance examination was reported positive. For two years he received mercury by injection.

* Received for publication October 24, 1940.

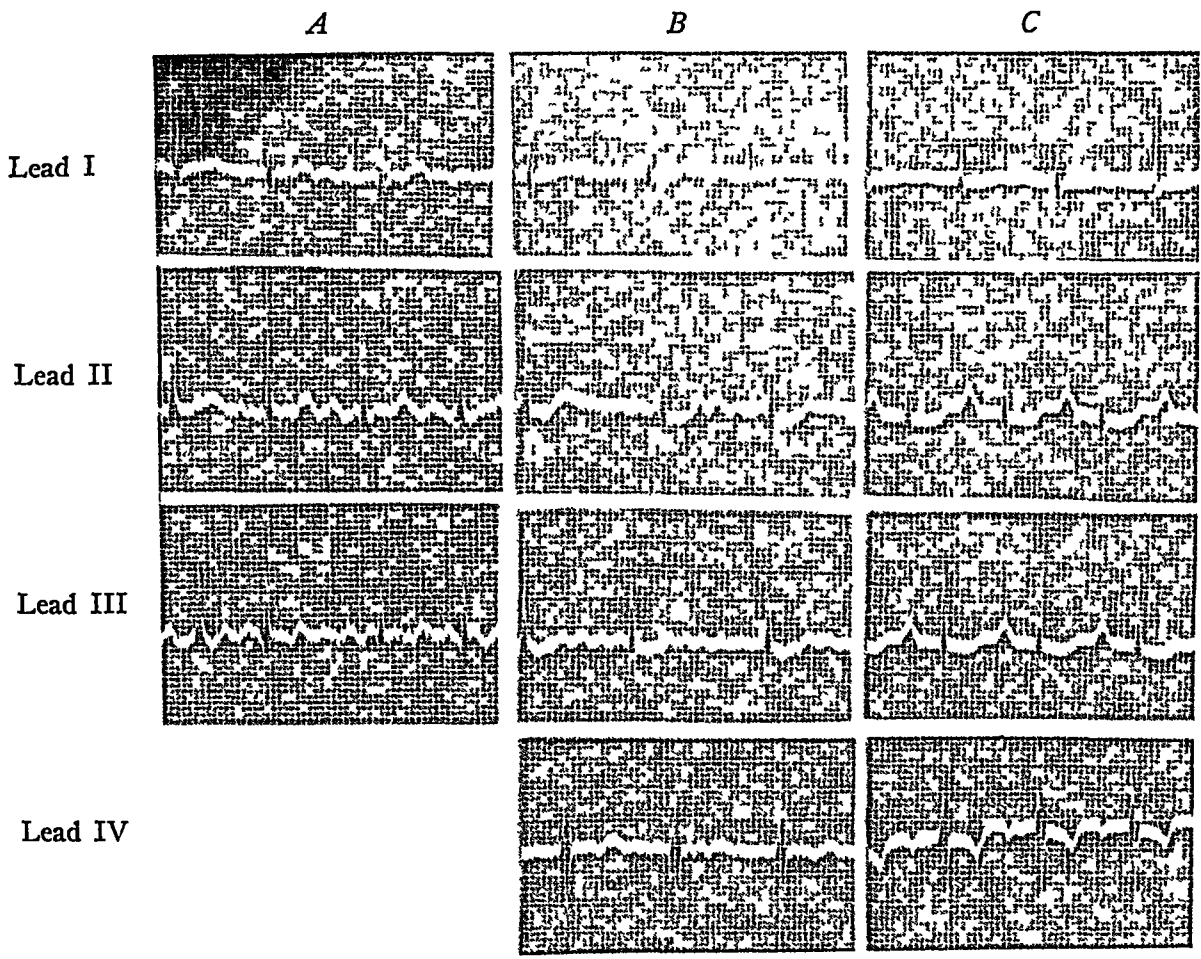


FIG 1

A April 1935, showing auricular fibrillation
B April 1939, preoperatively, showing auricular fibrillation
C May 1939, ten days after subtotal thyroidectomy, showing normal sinus rhythm and changes due to digitalis

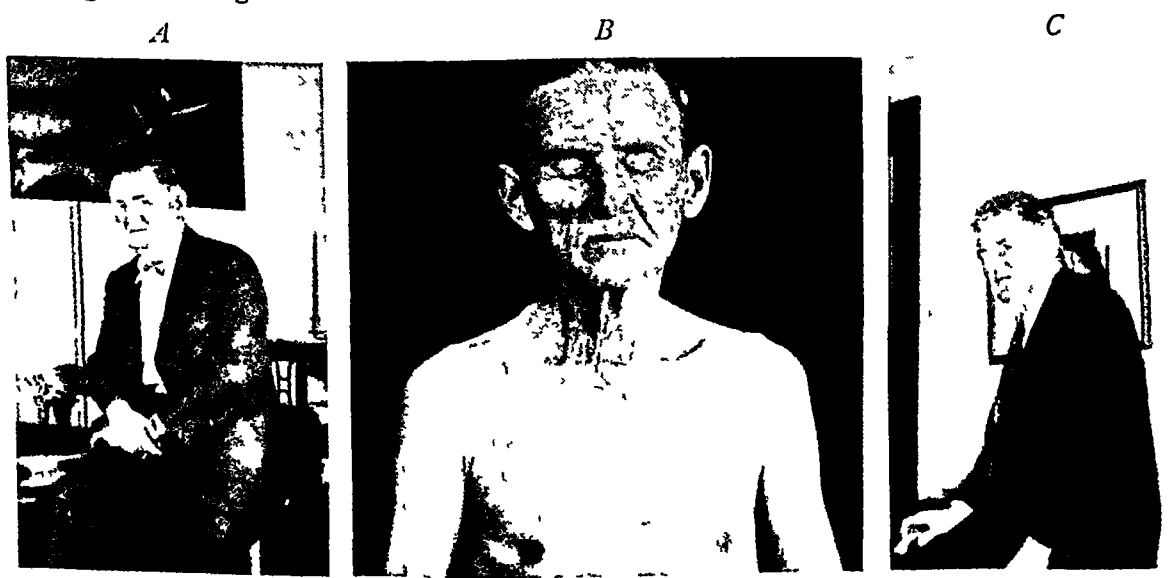


FIG 2

A 1931, weight 185 lbs (84 Kg)
B 1939, one week postoperative Weight 106 lbs (48.2 Kg)
C 1940, weight 160 lbs (73 Kg)

and the Wassermann reaction became negative and stayed so. Soon thereafter ulcerations appeared on the anterior and lateral surfaces of both legs. In the next 30 years these ulcerations disappeared and reappeared at varying intervals. No method of therapy, including varied ointments, ultraviolet light, or roentgen-ray was successful in curing the condition permanently. There were no other significant previous illnesses. He had been married and had one grown daughter. Tobacco and alcohol were used moderately.

Examination showed a well preserved man with moderate but definite emaciation (weight 134 pounds). His bodily movements were deliberate and somewhat slow, and he discussed his symptoms without any undue emotional color or overtone. There was no exophthalmos. The pupils reacted to light and accommodation. The gums were edentulous, and small normal tonsils were present. A small nut-sized nodule was palpable in the neck in the site of the right lateral lobe of the thyroid gland. The trachea was slightly deviated to the left. The lungs were clear. A large lipoma was present on the back over the right scapula.

The heart was not enlarged to percussion. The cardiac rhythm was completely irregular with a ventricular rate of 100 and a radial pulse rate of 90. A systolic murmur was heard at the apex, and the second aortic sound was louder than the second pulmonic sound. The systolic blood pressure was 120 and the diastolic 75 mm of Hg.

The liver was enlarged two fingers below the costal margin. No other significant abdominal findings were present. The genitalia and prostate were normal. All peripheral pulses were patent. The skin was loose and thin and normally moist. Over both lower extremities were wide areas of superficially ulcerated weeping sores and scarred skin representing healed lesions. A slight tremor of the extended fingers was present. There was no edema anywhere. The neurological examination was normal.

Laboratory Data. The blood count was normal. The blood Wassermann reaction was negative. Fluoroscopy visualized a normal cardiac silhouette. The thoracic aorta was somewhat elongated, and there was a prominent knob on the aortic arch. The lungs were clear.

After the ventricular rate had been reduced to 80 and the pulse deficit to two with digitalis, the basal metabolic rate was determined. The rate was plus 16 per cent (+16) on two occasions. Electrocardiogram (figure 1B) showed auricular fibrillation, depressed RT segments in the standard leads and a diphasic T. The segment changes were ascribed to the effect of digitalis.

The steady weight loss, the thyroid nodule, and the tremor of the outstretched fingers in combination with the auricular fibrillation, in spite of the comparatively normal metabolic rate, suggested the diagnosis of masked hyperthyroidism with cardiac manifestations, and subtotal thyroidectomy was proposed.

In anticipation of operation iodine therapy was begun. Ten minims of Lugol's iodine solution were given twice daily and a maintenance daily dose of three grains of digitalis leaf was continued. The patient decided to defer operation and discontinued the iodine for varying periods of time, resuming it again at will. He noted that his weight remained stationary while he took iodine. The cardiac rhythm was controlled with digitalis but remained completely irregular. The hepatomegaly disappeared.

He finally entered The Mount Sinai Hospital for operation in April 1939. The preoperative metabolic rate was plus 13 per cent (+13) and his weight was 123 pounds, a further loss of 11 pounds in eight months in spite of some medical therapy.

Under avertin and ethylene anesthesia a bilateral subtotal thyroidectomy was performed. The thyroid gland was found to be diffusely enlarged two and one half times normal size. It was situated posteriorly very deep in the neck where it could not have been palpable clinically. The trachea was deviated to the left.

For a few days postoperatively the patient did poorly, becoming very lethargic and apathetic. There was disorientation at times, and the pulse became extremely weak. Iodine was stopped, and stimulation with caffeine begun. This was effective, and

from that time convalescence was progressive. On the tenth postoperative day, the cardiac rhythm became regular with a rate of 85 (figure 1C). Digitalis was discontinued. Two weeks later the patient left the hospital.

Examination of the removed tissue was reported as follows: "On section these two thyroid lobes are similar in character and made up of numerous smaller distinct and separate nodes which are well encapsulated, alternately hemorrhagic and cellular, brown in color, containing a good deal of colloid and surrounded at the periphery by compressed relatively normal fleshy appearing thyroid tissue. The isthmus likewise contains a number of these nodules. Diagnosis: Macro- and microfollicular colloid adenoma."

In August 1939, four months after operation, the patient was examined. He weighed 148 pounds, a gain of 25 pounds, since the operation. His cardiac rhythm was regular with rate 88. The chronic ulcerated condition of his extremities had healed a few weeks after his discharge from the hospital and was still completely healed. There were no cardiac symptoms, and the patient felt completely normal.

In May 1940, the patient wrote from another city where he was living, "Feeling fine. Weight 160 pounds. Heart regular. Enclosing recent picture."

In May 1941 he reported by mail that his heart was regular, that he was maintaining his weight and that he was feeling very well.

COMMENT

In the case presented it is apparent that there were very few diagnostic aids. Aside from the auricular fibrillation which one so frequently encounters as evidence of coronary artery sclerosis in this age group, the only symptom which suggested a thyroid element was the steady weight loss over a period of years in spite of definite attention to food intake. Other clinical features which took on significance in retrospect were a very slight tremor of the extended fingers and a small thyroid nodule which could barely be palpated. The metabolic rate was minimally elevated ($+16$ per cent) and the fibrillation could be successfully controlled with the customary amounts of digitalis, features which were of no aid in establishing a diagnosis. With iodotherapy there was a retardation of the rate of weight loss but for the short period of time this drug was being administered no definite conclusions were warranted. Each of the foregoing manifestations alone could not be considered diagnostically significant, but in combination they produced a clinical syndrome that was fairly definite and that justified subtotal thyroidectomy.

Perhaps best proof of the eventual correctness of the diagnosis was the response to the surgical ablation of the thyroid gland. The spontaneous restoration of normal sinus rhythm 10 days after operation could occur in no other disease. Furthermore, the great weight gain immediately after operation and the disappearance of all signs and symptoms of cardiac insufficiency were additional proofs. An unexpected benefit, the rapid and permanent healing of the chronic leg ulcers, may be considered a sign of the metabolic changes induced in all the tissues of this patient by subtotal thyroidectomy.

THE AURICULAR FIBRILLATION

The patient presented one of the most characteristic cardiac manifestations of masked hyperthyroidism, i.e., auricular fibrillation. This was maintained un-

interruptedly for four years from April 1935 to May 1939. It was controlled easily with average doses of digitalis and was accompanied by varying degrees of myocardial insufficiency. The arrhythmia disappeared spontaneously 10 days after subtotal thyroidectomy, and the cardiac rhythm has remained normal since then, one year ago. Search of the literature has failed to find mention of a similar instance. In a series of 108 cases of auricular fibrillation in Graves' disease Barker, Bohning, and Wilson⁴ found an average duration of the arrhythmia of one year in the adenomatous group and 0.8 year in the exophthalmic group. These authors state that auricular fibrillation may appear before a significant elevation of the metabolic rate occurs. They observed spontaneous return to normal sinus rhythm in 53 per cent (28 cases) of the 53 who were operated upon. Anderson⁵ saw 32 per cent of 75 cases operated upon develop regular sinus rhythm. One case in this series had had auricular fibrillation for 20 years, but no indication is given in his paper whether or not his patient was included in the operated group. Hamilton⁶ reports an instance of auricular fibrillation for 12 years which, however, was not restored to normal sinus rhythm after thyroidectomy.

Ernstene⁷ likewise observed normal sinus rhythm reestablished in one-third of thyroidectomized patients with persistent fibrillation. Burch⁸ reports an instance of auricular fibrillation of 22 months' duration, but his patient did not have Graves' disease. A bibliography of similar cases may be found appended to his paper.

Of particular interest is the spontaneous resumption of normal rhythm after subtotal thyroidectomy. Now it is generally agreed that hyperthyroidism does not produce degenerative myocardial changes and that in an otherwise normal heart Graves' disease does not produce permanent heart muscle change. Thomas⁹ in a review of this subject states "if the hyperthyroidism is successfully terminated by subtotal thyroidectomy and adequate postoperative treatment is observed, the heart will sooner or later return to the state in which it was found at the beginning of the hyperthyroidism, allowing only for changes which would have occurred in a similar length of time under other conditions." Careful pathological studies have not confirmed earlier theories about changes in thyroid hearts. McEachern and Rake¹⁰ after an exhaustive examination of all the hearts of patients dying with hyperthyroidism at the Johns Hopkins Hospital concluded that no pronounced pathological change is produced in the heart of hyperthyroidism. With the removal of a thyroid factor that had caused a change in the cardiac rhythm for four years in this patient, the rhythm became normal. This would indicate quite emphatically that the thyroid factor had its effect only when present and that it had not caused any persisting alterations. Furthermore, there is in this case the suggestion that operation offers real chance of improvement in patients who have had the condition for many years and in those in whom the condition is not recognized until late.

THE CLINICAL PICTURE OF MASKED HYPERTHYROIDISM ASSOCIATED WITH HEART DISEASE

Masked hyperthyroidism as a cause of heart failure is relatively infrequent but, because of its amenability to therapy, extremely important to recognize. The cardinal signs of hyperthyroidism—an enlarged gland, tremor and exophthalmos—are usually absent, and there is often little to suggest that the pre-

senting picture of congestive heart failure with or without a cardiac arrhythmia has a thyroid basis. It must be remembered that the clinical picture is the result of an atypical or extremely mild hyperthyroidism usually with adenomata, acting on the heart for many years. Awareness of the existence of such cases will enhance diagnostic acumen and increase the frequency with which these patients are identified.

The syndrome occurs most frequently in women after middle life. Most often these individuals appear apathetic instead of hyperkinetic although there may be a noticeable alertness or rapidity in the manner in which they perform simple acts. Exophthalmos is extremely rare, but an ocular stare is not uncommon. The significance of the eye signs may be difficult to determine because of coexistent moderate to severe degrees of emaciation. The emaciation is caused by weight loss which may have continued slowly over a period of years in spite of adequate food intake and restricted activity. The edema resulting from heart failure may restore some of the body weight, but if sought for, a history of inexplicable but definite weight loss at some time is commonly obtainable. Rarely is this symptom absent. Fine tremor of the extended fingers may be observed, but too often this sign is not present. Pigmentation of the skin occurs. The thyroid gland may be normal to palpation, perhaps with a diffuse increased hardness. Diligent search will disclose small thyroid nodules in some cases. Other symptoms frequently associated with classical Graves' disease such as intolerance to heat, flushed moist skin, diarrhea, and general nervousness are not usual. The metabolic rate may be elevated, with figures surprisingly higher than the clinical impression would justify. Very often, however, there is only a moderate elevation in the metabolic rate from 10 to 20 per cent, and occasionally the metabolic rate is normal.

Because of the indistinct nature of the hyperthyroid symptoms and signs, the cardiac manifestations in masked hyperthyroidism dominate the clinical picture. To be mentioned in passing are simple tachycardia, with or without premature contractions, and paroxysmal tachycardia, cardiac manifestations which so often characterize cases of outspoken Graves' disease. Such variations in cardiac rate and rhythm do not occur frequently in masked hyperthyroidism.

More common and diagnostically significant is paroxysmal or maintained auricular fibrillation. This cardiac arrhythmia may be the only clue to the nature of the heart affection and point the way to the detection of the thyroid element underlying the clinical picture. Another lead to the etiology of the fibrillation is the great difficulty encountered in controlling the arrhythmia either intermittently or persistently. In such cases hyperthyroidism must be excluded, whether or not there is coexistent heart disease of another etiology.

Dyspnea, edema, and other signs of congestive failure may occur in long neglected, far advanced cases, but more generally these signs are determined by the extent of the underlying cardiac impairment upon which the hyperthyroidism acts as a precipitating and intensifying component. Dyspnea dissociated from paroxysmal arrhythmias is not common. Precordial pain may accompany the onset of paroxysmal fibrillation, or angina pectoris may be present independent of the arrhythmia.

In some instances the heart sounds possess an overacting quality which is so well heard in thyroid hearts with regular rhythm. Usually auscultation gives no special information aside from the arrhythmia although some authors describe a

forcible, short sudden apex beat, and systolic or pseudo-presystolic apical murmurs similar to those heard in active Graves' disease. Diastolic murmurs are not present and their absence helps to exclude frequently misdiagnosed mitral stenosis. The systolic blood pressure may be elevated. Fluoroscopic findings are determined by the duration of the hyperthyroidism. The older the case and the more extensive the involvement by arteriosclerosis or other types of heart disease, the greater the degree of cardiac enlargement. There is no characteristic cardiac contour in masked hyperthyroidism. The electrocardiogram confirms the totally irregular rhythm, but it is otherwise not remarkable.

In summary, the occurrence of auricular fibrillation, with or without cardiac failure in a middle aged patient who presents a definite degree of emaciation or a history of weight loss, presenting some of the clinical features enumerated above, should stimulate careful search for a hidden hyperthyroidism. The usual signs of hyperthyroidism, stroma, exophthalmos, tremor or elevated metabolic rate may not exist or if present, may be of insignificant degree. Organic heart disease of another etiology may coexist, but of itself is not the cause of the cardiac insufficiency or arrhythmia.

The outlook for this group of cases in spite of the fact that the patients are older and have usually had their disease for a long time is as favorable as for patients with active hyperthyroidism. From the standpoint of the cardiologist they afford an unusual opportunity for the radical removal of the cause of heart disease, an opportunity as desirable as it is rare. One must not be deterred by the apparent hopelessness of the condition in which these patients are found, or by the poor surgical risk they appear to present. Nothing can be expected from medical therapy and although hazardous, surgery should be undertaken in every case because of the excellent hope of real improvement and often of complete cure (Lahey¹¹). Of prime importance in the determination of the success or failure of the operation is the preoperative medical preparation. The signs of myocardial insufficiency must be reduced to a minimum by the use of the usual cardiotherapeutic measures, i.e., digitalis, diuretics, limitation of salt and fluid intake, rest and sedatives. If an arrhythmia such as fibrillation or more rarely flutter exists, it must be brought under maximum control with digitalis. Lugolization is accomplished in the same way as in the now routine preoperative treatment of Graves' disease. Some experience is required to select the most beneficial time for operation, and the active cooperation of surgeon and cardiologist produce best results. Lahey suggests that the operation always should be performed in two stages. Ethylene after preliminary narcosis with avertin is a favorable combination of anesthetics.

These cases may pursue an individual postoperative course also. If unfavorable, it is characterized by increasing apathy and preterminal coma, so different from the delirium and hyperactivity attending the death of a patient with obvious hyperthyroidism. Iodine should be discontinued after operation, and stimulation with caffeine or coramine begun when indicated.

SUMMARY

A case of masked hyperthyroidism with auricular fibrillation of four years' duration is described. Spontaneous resumption of normal sinus rhythm occurred 10 days after subtotal thyroidectomy.

The clinical syndrome of cardiac disease associated with masked hyperthyroidism is reviewed and discussed

REFERENCES

- 1 LAHEY, F H Thyroid operations in heart disease, *Surg Clin North Am*, 1934, xiv, 1225
- 2 LEVINE, S A Clinical heart disease, 2nd Ed, 1940, Saunders, Philadelphia
- 3 LEVINE, S A, and STURGIS, C C Hyperthyroidism masked as heart disease, *Boston Med and Surg Jr*, 1924, cxc, 233
- 4 BARKER, P S, BOHNING, A L, and WILSON, F N Auricular fibrillation in Graves' disease, *Am Heart Jr*, 1932, viii, 121
- 5 ANDERSON, J P Incidence of auricular fibrillation and results of quinidine therapy, *Am Heart Jr*, 1932, viii, 128
- 6 HAMILTON, B E The heart in toxic thyroid states, *Surg Clin North Am*, 1924, iv, 1411, 1924, iv, 1425 Thyroidism complicated by heart failure, *Jr Am Med Assoc*, 1923, lxxx, 1771
- 7 ERNSTENE, A C Cardiovascular complications of hyperthyroidism, *Am Jr Med Sci*, 1938, cxcv, 248
- 8 BURCH, G E Auricular fibrillation of 22 months' duration with return to normal sinus mechanism without aid of quinidine, *Am Heart Jr*, 1939, xviii, 102
- 9 THOMAS, H M The heart in hyperthyroidism, *ANN INT MED*, 1931, v, 184
- 10 MCEACHERN, D, and RAKE, G A study of the morbid anatomy of hearts from patients dying with hyperthyroidism, *Bull Johns Hopkins Hosp*, 1931, xlvii, 273
- 11 LAHEY, F H Surgical treatment of hyperthyroidism, *Bull New York Acad Med*, 1934, x, 65

GONOCOCCUS BACTEREMIA WITH JOINT AND SKIN MANIFESTATIONS; A CASE REPORT *

By RUTH C FOSTER, M D, *Madison, Wisconsin*

THE following case is reported because it represents a syndrome characterized by fever, joint pains and rash typical of certain gonococcal bacteremias. It was undiagnosed before the laboratory isolated the organism from the blood stream, but it is probable that the case could have been diagnosed from the clinical course alone and proper therapy started at once. Several similar cases have been reported by Wheeler and Cornell,⁶ Rubenstone,⁷ Cabot,¹ Filler,³ and Keil.⁵ The following case report is identical in many ways to these reported cases.

CASE REPORT

A 20-year-old white female was admitted to the University of Wisconsin Student Infirmary on December 23, 1939 because of a chief complaint of "sore joints." She had felt well until December 20 when she developed multiple joint pains, stiffness, generalized muscle soreness and a temperature of 99.4° F. The following day the temperature was 101° F accompanied by general malaise and increased pain involving the fingers, wrists, shoulders and knees.

The history by systems revealed nothing of significance.

* Received for publication July 21, 1941

The past medical history was of interest because, following a slight cold in January 1937, the patient was hospitalized due to pain in the shoulders, wrists and fingers. At that time the only pertinent findings were a soft systolic murmur along the left sternal border disappearing with deep inspiration, and a rapid sedimentation rate. Numerous electrocardiograms were normal except on one occasion when the P-R interval was 0.21 second. The impression was that this may have been a mild rheumatic fever although later cardiac examinations revealed no pathology. Occasional joint pains persisted until the present illness.

The physical examination revealed a well developed and nourished patient not acutely ill. There was tenderness of the left hand, wrist and shoulder, and of the right knee, but no redness or swelling was present. There were bilateral diseased tonsil tags. The cardiac examination revealed a soft blowing systolic murmur along the left sternal border similar to that heard upon previous examinations. The pulse was 88, blood pressure 120 mm Hg systolic and 82 mm diastolic, and the temperature 98° F. The liver and spleen were not palpable. The leukocyte count was 8,650 with a normal differential, the sedimentation rate was 18 mm and the electrocardiogram was normal. There was a daily febrile reaction of 99.2° F but the pains rapidly subsided and on December 27 the patient had no complaints. However, on this date it was observed that the white cell count had risen to 13,850 with 74 per cent neutrophils.

On the afternoon of December 28 there was stiffness of the joints. On the morning of December 29, nine days after the onset of the illness, there were chills, "pain all over the body" and a temperature of 104.2° F. The physical examination showed an acutely ill and uncomfortable patient with exquisite tenderness over the dorsal spine and both shoulder joints. The white cell count was 21,900 with 85 per cent neutrophils. By evening the temperature started to fall. At this time a few discrete reddish-purple maculopapular lesions about 0.3 mm in diameter appeared over the extensor surface of the forearms, hands, legs and chest. The following morning these had a hyperemic base with a small vesicle in the center. Several of the vesicles had a hemorrhagic appearance. The patient then recalled having had a similar rash with the first attack of fever and joint pains, December 23, 1939.

The above symptoms subsided within 24 hours. The white cell count fell to 11,300 and there was apparent convalescence until January 4, six days after the exacerbation of symptoms, when there was another attack similar to that described above. A maculopapular eruption again appeared, this time on the chest, back and arms. The lesions were identical to those noted previously. A few later developed vesicles. There was some swelling of the fingers of the left hand, the first occasion on which swelling was present. The temperature reached 102.4° F and the white cell count 24,550.

On January 8, four days after this attack, there were gas pains and excruciating pain in the right lower quadrant and right chest associated with vomiting and several liquid stools. The patient appeared very ill, obviously nauseated and in great pain. Her temperature was 102.4° F, the white cell count 43,450 with 93 per cent neutrophils, but no physical findings suggested pathology in the chest or abdomen.

Because of the episode of fever, joint pains, and the simultaneous appearance of the rash described, blood cultures were taken with the first febrile reaction December 29. These showed no growth in 24 hours but by January 4 a gram negative diplococcus was isolated which was later identified as the gonococcus. The patient denied exposure to gonorrhea. A pelvic examination revealed a slight urethritis but no pelvic pathology. Smears from the urethra were positive for gonococci, but smears from the cervix and vagina were negative for this organism.

On January 8 it was felt that the diagnosis in this case was gonococcal bacteremia. The patient was acutely ill and too nauseated to be given oral medication. At 12.45

p m she was given 3 grams of Promin intravenously By 4 00 p m the temperature had dropped to 99 6° F and all gastrointestinal symptoms had subsided The following morning sulfanilamide grains 80 daily was started This was given for two days followed by 60 grains daily for three days and 40 grains daily for six days The temperature remained normal and the patient was free from all symptoms after the second day of medication Repeated smears and blood cultures were negative

This individual has been followed for 18 months There has never been an exacerbation of her symptoms nor has she had a recurrence of the muscle pains noted during the two years previous to her illness Repeated cervical, vaginal and urethral smears have been negative for the gonococcus

DISCUSSION

Typically, patients with this syndrome have a remittent fever although the course is not so characteristic as the double quotidian temperature frequently seen in gonococcal endocarditis This patient had a febrile reaction about every six days (figure 1), suggesting the possibility that the fever caused a tem-

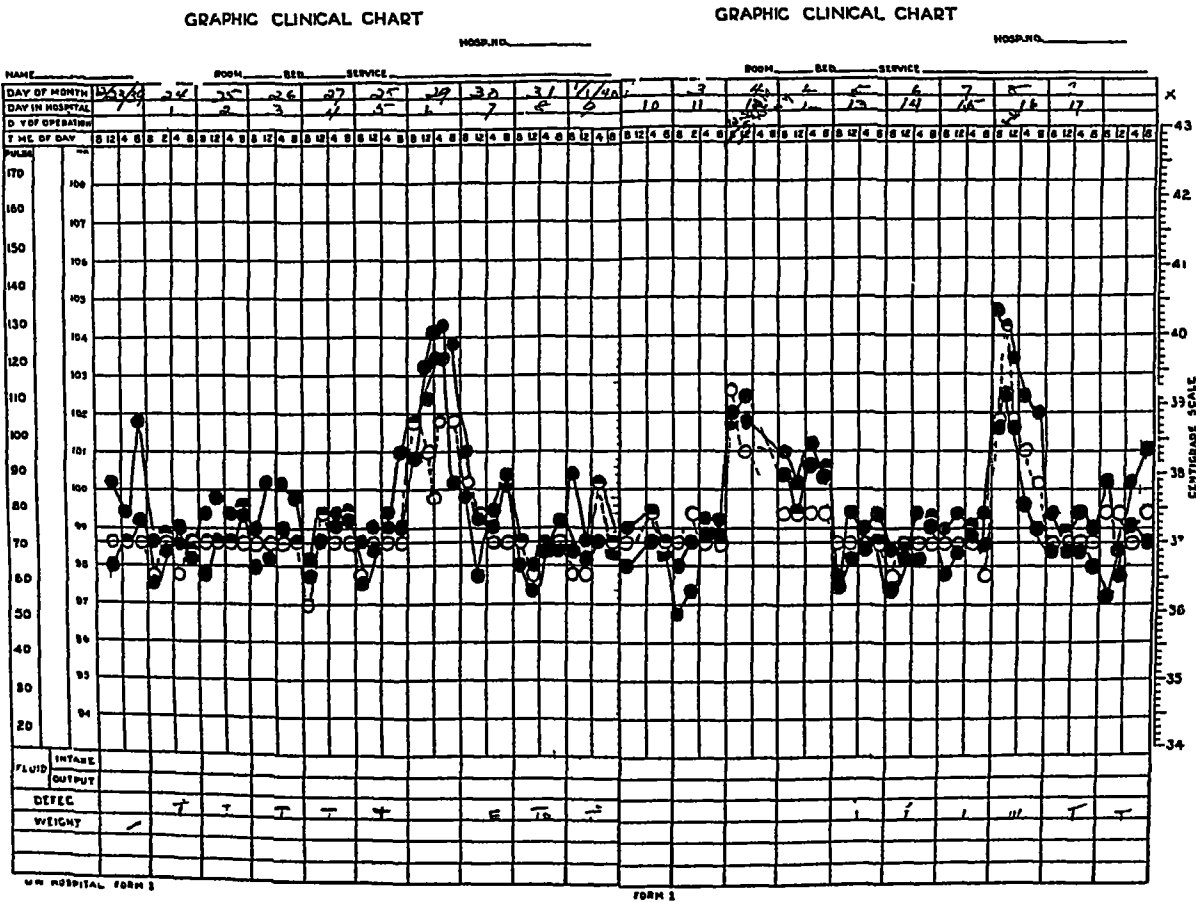


FIG 1

porary sterilization of the blood stream However, sufficient blood cultures were not taken to establish this fact

In these cases joint pains may or may not be localized and frequently there is swelling with local redness of the joints Keil⁵ reports two cases which began with a sore throat so it is not surprising that the condition is frequently

mistaken for rheumatic fever. However, it fails to respond to salicylates and the electrocardiogram shows no findings characteristic of rheumatic fever. This patient received large doses of salicylates without relief. Repeated electrocardiograms taken during her illness were normal.

The skin lesion is the characteristic feature. Gonococcal eruptions are classified as (1) Erythemas, (2) urticaria and nodosal lesions, (3) hemorrhagic and bullous lesions, and (4) hyperkeratoses.¹ In 1938 Keil² described five cases of gonococcal bacteremia without endocarditis and with a characteristic hemorrhagic vesiculopustular lesion. He stated that these lesions are discrete, are not extensive in distribution and that they have a tendency to occur in crops, especially during a febrile period. They start as "an erythematous macule that acquires a central vesicle or pustule."³ Not infrequently a hemorrhage occurs in the center of the lesion and occasionally organisms are present in the vesicle. This case had erythematous lesions, many of which became vesicular, a few later developing hemorrhagic centers. The lesions appeared in crops with each febrile reaction.

The patient showed no evidence of endocarditis nor did those cases described by Keil.² Davis³ has stated that in gonococcal septicemia cutaneous lesions usually indicate an infection of the blood stream in the absence of a complicating endocarditis. Patients with a gonococcal bacteremia without endocarditis have a good prognosis. The course may be prolonged, in some perhaps for years. Because of repeated denials of exposure it is impossible to state when our patient developed her original infection. It is interesting that she had atypical joint pains for two years without a true endocarditis and that she has had no joint pains in the 18 months following the acute illness. Whether she had had an old gonococcal infection with a recent exacerbation is unknown. Frequently the local focus in these cases is never found and no history is obtained to indicate a gonococcus infection.

In this individual the response to the sulfonamides was spectacular. Within three hours after the intravenous Promin the patient was afebrile and asymptomatic. There has never been a recurrence. There was delay in giving the drug because of the time required to isolate the organism from the blood stream and identify it. Unfortunately, in many of these cases the organism is not isolated. In the latter group it is important to recognize the syndrome of joint pains, fever and vesicular rash so that therapy may be instituted.

SUMMARY

A case of gonococcal bacteremia characterized by fever, joint manifestations and a vesicular dermatitis is presented and discussed. The response to the sulfonamides was immediate.

BIBLIOGRAPHY

- 1 CABOT, RICHARD C. An obscure general infection, *Boston Med and Surg Jr*, 1927, cxcvii, 1141.
- 2 DAVIS, JOHN S. Diagnosis and treatment of gonorrheal septicemia and gonorrheal endocarditis, *Arch Int Med*, 1940, lxi, 418.
- 3 FILLER, WILLIAM. Gonococcemia with recovery, *Jr Am Med Assoc*, 1933, c, 1149.

- 4 FUTCHER, PALMER HOWARD The double quotidian temperature curve of gonococcal endocarditis A diagnostic test, *Am Jr Med Sci*, 1940, cxcix, 23
- 5 KEIL, HARRY A type of gonococcal bacteraemia with characteristic haemorrhagic vesiculopustular and bullous skin lesions, *Quart Jr Med*, 1938, vii, 1
- 6 OSLER, WM, and McCRAE, THOMAS *Modern medicine*, 1913, i, 743
- 7 RUBENSTONE, A I, and ISRAEL, S Gonococcemia with recovery, *Jr Am Med Assoc*, 1932, xcix, 1685
- 8 WHEELER, G W, and CORNELL, N W Gonococcal bacteremia in a woman with apparent cure by surgical intervention, *Jr Am Med Assoc*, 1930, xciv, 1568
- 9 WILLIAMS, ROBERT H Gonococcic endocarditis A study of twelve cases with ten post-mortem examinations, *Arch Int Med*, 1938, lxi, 26

EDITORIAL

LYMPHOCYTIC CHORIOMENINGITIS AS A SYSTEMIC DISEASE

CASES presenting the clinical syndrome later designated as lymphocytic choriomeningitis were first described by Wallgren (1935) under the term acute aseptic meningitis. These cases presented the picture of an acute febrile infection accompanied by manifestations of meningeal irritation. They all recovered after a short illness without sequelae. The cerebrospinal fluid showed a well marked increase in lymphocytes but yielded sterile cultures. Recognized conditions which may cause similar reactions in the cerebrospinal fluid, such as tuberculous meningitis or poliomyelitis, could be excluded.

In 1935 Rivers and Scott¹ isolated from the cerebrospinal fluid of two such cases a filtrable virus which has since been known as the virus of lymphocytic choriomeningitis. This was quickly found to be identical with two strains of virus previously isolated—one by Armstrong and Lilje (1934) from a monkey, the other by Traub² (1935) from a colony of white mice. Since that time 35 cases of the disease have been reported^{3, 4} which have been proved to be caused by this virus. These 35, however, make up less than a third of the cases designated as acute septic meningitis which have been adequately investigated. Some of the other cases have yielded viruses antigenically different, but in many the cause could not be determined.

Although the small number of proved cases suggests that the disease is rare, it has been found widely distributed in the United States. The virus has been reported from England, France and Japan and is probably distributed throughout the world. More recent investigations indicate that the infection is much commoner than these figures would suggest.

The virus can be demonstrated by the inoculation of susceptible animals. Mice and guinea pigs are most suitable, although monkeys are also susceptible. Mild or symptomless infections can be produced in several other species, including dogs. If cerebrospinal fluid or other infectious material is injected intracerebrally into mice, after an incubation period of about six days the mice become acutely ill, are prostrated and display clonic generalized convulsions with spasticity and hyperextension of the hind legs. Most of the mice die within a day or two. They show an intense infiltration of lymphocytes in the meninges and choroid plexus, but there are only minimal changes in the brain substance. They often also show interstitial pneumonia,

¹ RIVERS, T. M., and SCOTT, T. F. M. Meningitis in man caused by a filtrable virus, *Science*, 1935, **LXXXI**, 439.

² TRAUB, E. A filtrable virus recovered from white mice, *Science*, 1935, **LXXXI**, 439.

³ ARMSTRONG, C. R. Studies on choriomeningitis and poliomyelitis, *Harvey Lectures*, 1940-41, 39-56.

⁴ FARMER, T. W., and JANEWAY, C. A. Infections with the virus of lymphocytic choriomeningitis, *Medicine*, 1942, **XVI**, 1-63.

pleural effusions, and focal necroses in the liver, changes which indicate the generalized nature of the infection. The virus is present in these organs and in the blood. Similar lesions have been described in man in a few cases corresponding clinically to lymphocytic choriomeningitis, but there has as yet been no autopsy reported on a human case in which the virus was positively identified.

Those mice which survive recover completely, become free of virus and are specifically immune to reinfection. Mice also become immune following subcutaneous or intraperitoneal inoculation, although the infection so produced is usually mild or symptomless. Resistance to reinfection develops within a few days, although in this species no neutralizing antibodies have been demonstrated in the blood. This specific immunity makes possible the positive identification of a newly isolated strain of virus, by demonstrating that the latter causes typical symptoms in normal mice, but causes no infection in mice which have been immunized with a known strain of lymphocytic choriomeningitis virus.

There is much evidence that mice constitute the natural reservoir of the virus and that infection in man is acquired by contact with the secretions or excreta of such infected animals. Traub^{2, 5} has reported an extensive study of the disease as it developed spontaneously in a colony of white mice. The infected mice transmitted the virus to their young in utero. Young mice often showed symptoms of illness but usually made a clinical recovery. Older mice rarely showed any evidences of infection. The virus, however, continued to be present in the blood, brain and other organs and was excreted in the nasal secretions, urine and feces throughout life.^{6, 7} Under these conditions the mice appeared to develop a tolerance for the virus rather than an immunity, since traumatization of the brain, for example by intracerebral inoculation of sterile broth, will precipitate a severe and often fatal attack of encephalitis.

Gray house mice are also susceptible. They may carry the virus in their blood and tissues for months without manifest illness, they may convey it to the young in utero⁴ and they excrete it in the urine and feces. Many naturally infected mice have been trapped. Armstrong and his associates³ have shown that there is a close association between the natural infection in house mice and cases of human infection. They reported capturing infected mice in the homes of five out of six cases of lymphocytic choriomeningitis. Farmer and Janeway⁴ have reported similar observations.

Guinea pigs can be infected about equally well by subcutaneous, intraperitoneal or intracerebral inoculation. After two to four days they show evident malaise, anorexia, emaciation, prostration and respiratory distress. Many die during the second week and show extensive visceral lesions, particularly interstitial pneumonia, as well as lymphocytic infiltration of the meninges. The virus is present in the blood and tissues generally. Am-

⁵ TRAUB, E. Epidemiology of lymphocytic choriomeningitis in a mouse stock observed for four years, *Jr Exper Med*, 1939, **111**, 801.

imals which recover quickly develop resistance to reinfection and after a longer interval show virus-neutralizing antibodies in their blood

Man is also susceptible to inoculation. Lépine et al.⁶ gave subcutaneous inoculations of infected mouse brain emulsion to a series of volunteers. After an incubation period of two to three days fever developed, usually accompanied by prostration, malaise and general aching, clinically resembling "grippe". Virus was demonstrable in the blood. The fever usually lasted two to three weeks, but was often interrupted by one or two remissions. In about half the cases meningitis then developed, and the virus could be isolated from the cerebrospinal fluid. The others recovered without showing evidence of central nervous system involvement. In both groups neutralizing antibodies later appeared in the blood. The experimental infection in man, therefore, often runs its course without manifestations of meningeal involvement.

Epidemiological observations and immunological studies early led to the belief that this is also true of spontaneous human infections. Patients who recover from the disease, after two to three months, show specific neutralizing antibodies in their serum which may persist for several years. The presence of such protective power is regarded as proof of recovery from the infection.

In 1935 Armstrong and Wooly noted neutralizing power in the serum of an attendant who cared for infected animals, although he gave no history of meningitis, and they regarded this as probably the result of a systemic infection. Traub also reported the development under observation of antibodies in an attendant similarly engaged, who showed no clinical evidence of meningitis.

Since then Armstrong and his associates⁷ have reported studies of 1000 sera from individuals without a history of any disease of the central nervous system, of which 10 per cent showed definite neutralizing power. Yamarat (quoted by Farmer and Janeway⁴) found 12 per cent positive among 126 miscellaneous patients in Boston. Armstrong also reported 26 per cent positive among 106 cases selected because of a history of recent upper respiratory tract infection. Direct proof of the occurrence of such spontaneous abortive cases was first brought by Armstrong and Hornibrook.⁷ This was in a laboratory worker who had an acute illness with fever of a week's duration, malaise, backache, prostration and leukopenia, but showed no sign of meningitis. Virus was obtained from the blood. Before the illness the blood had shown no protective power, but six weeks later it was highly active.

These observations indicate that the infection is much more common than has been supposed, and that a large proportion of the cases are not recognized because they are virtually symptomless or present the indistinctive

⁶ LEPINE, P, MOLLARET, P, and KREIS, B. Réceptivité de l'homme au virus murin de la choriomeningite lymphocytaire, reproduction expérimentale de la meningite lymphocytaire bénigne, *Compt rend Acad. d sci*, 1937, cciv, 1846.

⁷ ARMSTRONG, C R, and HORNIBROOK, J W. Choriomeningitis virus infection without central nervous system manifestations, report of a case, *Pub Health Rep*, 1941, lvi, 907.

features of an ordinary "grippal" or upper respiratory infection. The older conception of the clinical features of the disease must be changed. After an incubation period of five to 10 days following exposure the disease starts abruptly with manifestations of a generalized systemic infection. There is fever, often undulant in type, prostration, anorexia, malaise and aching of a grippal type. Occasionally there are symptoms of an upper respiratory infection. The virus can be demonstrated in the blood which shows a leukopenia and granulocytopenia. In many cases, probably in a large majority, the fever subsides after from one to three weeks and the patient recovers completely.

In other cases, often after a brief remission, there is an abrupt recurrence of fever with severe general headache, backache, nausea, vomiting, and often some degree of drowsiness or mental disturbance. There are signs of meningeal irritation—a stiff neck, often photophobia, a positive Kernig sign and localized reflex disturbances, occasionally papilledema. The leukocyte count is normal or moderately elevated, the sedimentation rate is usually normal. The virus usually disappears from the blood at this time, but it can be obtained from the cerebrospinal fluid. The latter is clear or slightly opalescent, the pressure is often elevated, the protein content increased, and the cell count is increased, usually from 60 to 3000 per cu mm, of which nearly all are lymphocytes. The fluid is usually normal in all other respects. After from one to four weeks as a rule the patient recovers completely. There may be considerable loss of weight and weakness and convalescence may be protracted.

In rare instances, as in two cases reported by Findlay et al,⁸ there may be an encephalitis. These cases show more profound mental disturbances, paralyses, gross reflex disturbances, and paresthesias or anesthetics. Recovery appears to follow as a rule, but there may be permanent sequelae. A few cases probably of this nature have come to autopsy, but the identity of the virus was not definitely established. The disease is not invariably benign.

The diagnosis can be established only by isolation and identification of the virus, or by demonstrating protective power (or other evidence of immune bodies) in the serum after recovery. Both are cumbersome procedures, possible only in well equipped laboratories. It is obvious that the diagnosis is rarely made or even suspected in cases showing only a systemic infection. Smadel,⁹ however, has perfected a complement fixation technic which should be very useful for such work if its reliability is confirmed. A systematic study of cases of "influenza" and "atypical" pneumonia as well as aseptic meningitis would be desirable to determine the frequency and practical importance of the disease.

⁸ FINDLAY, G. M., ALCOCK, N. S., and STERN, R. O. The virus etiology of one form of lymphocytic meningitis, *Lancet*, 1936, 1, 650.

⁹ SMADAI, J. E., BAIRD, R. D., and WALL, M. J. Complement fixation in chorio-meningitis. *Proc. Soc. Exper. Biol. and Med.*, 1939, 41, 71.

REVIEWS

Chinese Lessons to Western Medicine A Contribution to Geographical Medicine from the Clinics of Peiping Union Medical College By I SNAPPER, M D , foreword by GEORGE R MINOT, Professor of Medicine, Harvard University 380 pages, 16 X 24.5 cm Interscience Publishers Inc, New York 1941 Price, \$5.50

The occidental clinician will find in this brief volume an excellent introduction to the many special problems encountered in the practice of clinical medicine in North China. From the wards of the Peiping Union Medical College Hospital, Dr Snapper has chosen material covering the entire range of internal medicine. Of chief interest to the Western clinician is the demonstration of geographical influence upon disease. The social and economic environment peculiar to this region likewise are shown to have their influence upon the manifestations of disease. Nutritional problems pervade every clinical picture and are ably discussed here. Numerous case abstracts are presented throughout the volume. All modern technics of study are fully utilized. Numerous original illustrations increase the value of the clinical presentations. Of particular interest are the sections devoted to such parasitic diseases as Kala-Azar and Schistosomiasis. Dr Snapper has approached these subjects with an exceptionally broad background of clinical teaching and investigation. The material is presented in a manner calculated to hold the attention of the most discriminating reader.

M S S

Brucellosis (Undulant Fever), Clinical and Subclinical By HAROLD J HARRIS, M D 305 pages, 24 X 16 cm Paul B Hoeber, Inc, N Y 1941 Price, \$5.50

This book is a concise practical treatise on brucellosis written by a practitioner and health officer especially for those whose interest lies in the management of this disease. The author has turned to the knowledge and experience gained through his personal contact with the disease to corroborate or refute the conclusions arrived at through a careful review of the literature.

Aside from a well-organized presentation and critical evaluation of diagnostic procedures and therapy, he has included chapters on the pathology, public health aspects as well as the medico-legal side of this disease.

This monograph evidences a thorough knowledge of the subject presented and a careful evaluation of the many difficulties encountered in diagnosis and treatment. The results of his personal experiences should prove of great value. Carefully planned, delightfully written, well-illustrated and attractively bound, it should prove a welcome addition to the working library of every physician.

J A W

Diseases of the Nails By V PARDO-CASTELLO, M D , foreword by HOWARD FOX, M D 2nd Ed 193 pages, 14.5 X 23.5 cm Charles C Thomas, Springfield, Ill 1941 Price, \$3.50

Pardo-Castello's new textbook on Diseases of the Nails is a second edition of this useful monograph. Most of the 94 photographs are excellent and so supplement the text that the average reader can clearly grasp the pathologic changes which are described. The paper is excellent and the large clear type is very readable. The frequent use of the abused term, eczema, again demonstrates the need of an authori-

tative committee to define eczema or replace it by some acceptable term. The unscientific term ringworm is used too frequently in this technical text. The author has omitted some acceptable facts, such as the rapid and favorable response of granuloma pyogenicum to roentgen therapy. The second edition of this monograph brings up to date the only English symposium on diseases of the nails and should serve as an excellent reference for the physician and student interested in this subject.

F A E

COLLEGE NEWS NOTES

THE ST PAUL SESSION OF THE COLLEGE

The 26th Annual Session of the American College of Physicians, held in St Paul, Minn., April 20-24 1924, excelled all reasonable expectations. Although the gross attendance was smaller than during the last four or five years, it was nevertheless gratifying when one considers the location of the meeting city with respect to the center of population and the attendant war conditions. There were in attendance 1368 physicians, 75 medical students, 243 non-physician guests and 162 visiting wives or daughters of attending members, total 1848. The gross attendance from the leading states was as follows:

Minnesota	652	Michigan	66
Illinois	124	Wisconsin	66
Pennsylvania	101	Ohio	60
New York	99	California	45

The only states not represented were Idaho and Nevada. From Canada 25 were in attendance. Puerto Rico, Mexico and Argentina were represented.

Physical accommodations for the General Sessions, Panel Discussions, Clinics and Technical Exhibits were excellent, and everyone in attendance was able to obtain admittance to any program in which he was interested.

The entire program was marked by its outstanding excellence, and very few speakers were absent because of the war, although more than 12 per cent of the College membership is now on active military duty.

At the Convocation on Wednesday evening, April 22, 302 physicians were inducted to Fellowship, coming from 41 different states, the Medical Corps of the U S Army, the Medical Corps of the U S Navy, the U S Public Health Service, 2 provinces of Canada, from Panama and China.

The Ramsey County (Minn.) Medical Society, as host to the College, presented an excellent program of entertainment on Tuesday evening, April 21. It is regretted that the attendance at this particular function was small owing to the fact that the Annual Session program was so full that many members of the College overlooked this special feature.

The local Ladies' Entertainment Committee, with characteristic St Paul hospitality and graciousness, entertained the 162 visiting women at numerous special functions.

The Annual Banquet, though not largely attended this year, was a festive occasion, and the guests were entertained by addresses by the President, the President-Elect and the speaker of the evening, Dr William A. O'Brien, Director of Post-graduate Medical Education at the University of Minnesota, who gave many interesting and entertaining stories connected with "Medicine and the Public."

The Exposition and Technical Exhibit, though somewhat reduced in scope due to the high standards set by the College, was on a high, scientific and educational scale, and again merited the respect and the applause of all visiting physicians.

Dr Roger I. Lee, of Boston, retired as President, Dr James E. Paullin, of Atlanta, President-Elect, was inducted to office as President, Dr Ernest E. Irons, of Chicago, was named President-Elect for the coming year. Dr Charles H. Cocke, of Asheville, for many years Chairman of the Board of Governors of the College, was elected First Vice President. In appreciation and lasting recognition of Dr Cocke's long and faithful service as Chairman of the Board of Governors, the Board unanimously voted that a silver ferruled gavel, engraved appropriately, be prepared and presented to Dr Cocke. Dr Henry R. Carstens, of Detroit, for many years



JAMES E PAULLIN

PRESIDENT, AMERICAN COLLEGE OF PHYSICIANS, 1942-43

College Governor for Michigan, was elected Second Vice President, and Dr A C Griffith, of Kansas City, for many years College Governor for Missouri, was elected Third Vice President. Dr William B Breed, Boston, was unanimously elected Chairman of the Board of Governors and thereby becomes ex officio a member of the Board of Regents. Dr Chauncey W Dowden, Louisville, continues as the Vice-Chairman of the Board of Governors.

Dr Francis G Blake New Haven, Dr Reginald Fitz, Boston, and Dr Charles T Stone Galveston, were reelected for a term of three years on the Board of Regents. Also elected to the Board of Regents was the retiring President, Dr Roger I Lee, of Boston, and Dr James F Churchill of San Diego.

Dr Robert O Brown Santa Fe, was elected Governor for New Mexico, succeeding the late Dr LeRoy Peters. Among other new elections to the Board of Governors were Dr Gilbert M Stevenson, Ancon, Governor for Panama and the Canal Zone, Dr Benjamin F Wolverton Cedar Rapids, Governor for Iowa, Dr Edgar Hull, New Orleans, Governor for Louisiana, Dr Douglas Donald, Detroit, Governor for Michigan, Dr Ralph Kinsella, St Louis, Governor for Missouri, Dr Harry T French, Hanover Governor for New Hampshire, and Dr Paul F Whitaker, Kinston Governor for North Carolina.

The personnel of new committees will be published in a succeeding issue of this journal as will also the Minutes of the Board of Regents and of the Board of Governors.

JAMES E PAULLIN, M D

JAMES E PAULLIN, M D, President-Elect, 1941-42, and President, 1942-43, American College of Physicians, born, Fort Gaines, Ga, November 3, 1881, A B, Mercer University, 1900, continuing as graduate student through 1901, LL D (honorary), Mercer University, 1929, M D, Johns Hopkins University School of Medicine, 1905, Resident Pathologist, Rhode Island Hospital, Providence, 1905-06, Resident, Piedmont Hospital, 1906-07, Pathologist, Georgia State Board of Health, 1907-11, Associate Professor of Pathology, Atlanta College of Physicians and Surgeons, 1907-11, Associate Visiting Physician, Grady Hospital, 1909-13, Visiting Physician and Chief of the Emory University Division, Grady Hospital, Atlanta, Professor of Clinical Medicine, Emory University School of Medicine since 1915. Major, Medical Corps, U S Army, 1918-19, serving as Chief of Medical Service, Camp Shelby, Miss. Former President (1913), Fulton County (Ga) Medical Society, formerly President, Medical Association of Georgia, Member and former Chairman of the Medical Section, Southern Medical Association, Chairman of the Medical Section (1927), Chairman of the Council on Scientific Assembly (1939) and at present Member of the Medical Preparedness Committee, American Medical Association, former President (1937), American Clinical and Climatological Society, Member of the Association of American Physicians, Fellow of the American College of Physicians since 1928, serving for several years as Regent and Chairman of various Committees, Member of the Procurement and Assignment Agency, Office of Defense Health and Welfare, Federal Security Administration, Member of Sigma Nu, Phi Chi and Alpha Omega Alpha fraternities, Presbyterian, Member of the Capital City and Piedmont Driving Clubs, author of many papers published in the Journal of the Medical Association of Georgia, Southern Medical Association Journal, Journal of the American Medical Association, Annals of Internal Medicine, etc. guest Professor of Medicine for one week at the Peter Bent Brigham Hospital in 1936 and Physician-in-Chief pro tempore at the Pratt Diagnostic Clinic of Tufts College Medical School, Boston.



ERNEST E IRONS

PRESIDENT-ELECT, AMERICAN COLLEGE OF PHYSICIANS, 1942-43

ERNEST E IRONS, M D

ERNEST E IRONS M D, 122 S Michigan Ave, Chicago, Ill Born, Council Bluffs, Iowa, 1877, S B University of Chicago, 1900, M D, Rush Medical College, Chicago, 1903, Ph D, University of Chicago, 1912, Postgraduate work at the University of Vienna, 1909-10, Fellow in Bacteriology, University of Chicago, 1900-01, Assistant in Bacteriology, same 1901-03, Internship at Presbyterian Hospital, Chicago, Assistant to Dr James B Herrick, widely known and revered Internist and Cardiologist of Chicago, 1905-12 served during World War I as Lieutenant Colonel in the Medical Corps of the U S Army, Member of the Council on Pharmacy and Chemistry of the American Medical Association, 1923-40, Dean, Rush Medical College, Chicago 1923-36, Charter Member of the American Board of Internal Medicine since 1936 and Chairman of same since 1940, Rush Professor of Medicine, University of Illinois Medical School, Attending Physician, Presbyterian Hospital, Fellow of the American College of Physicians since 1929, and a member of its Board of Regents active on its various Committees since 1938, Member of the Chicago Medical Society, Illinois State Medical Society Association of American Physicians, American Society for Clinical Investigation Central Society for Clinical Investigation, Chicago Pathological Society, American Association of Pathologists and Bacteriologists, American Association for Study of Rheumatic Diseases, and others, author of many published papers

THE 1942 ANNUAL BUSINESS MEETING

The General Business Meeting of the American College of Physicians convened at St Paul, Minn, Thursday, April 23, 1942, with President Roger I Lee presiding and Mr E R Loveland acting as Secretary The Secretary read abstracted minutes of the preceding Annual Business Meeting, which were approved as read

The Treasurer, Dr William D Stroud, presented the following report

"The finances of the American College of Physicians are under the general supervision of its Board of Regents and more specifically supervised by the Committee on Finance The accounts are recorded in the Executive Offices according to accepted accounting principles and audited by a Certified Public Accountant

"1941 operations indicate a satisfactory financial situation The Endowment Fund on December 31, 1941, amounted to \$132,586 38, the General Fund to \$166,323 61, making the total College assets at book value \$298,909 99 The net increase in capital for both Funds was \$25,641 29 Full detailed financial statements will be published in an early issue of the ANNALS OF INTERNAL MEDICINE for the information of all members

On the recommendation of the Finance Committee and the subsequent approval of the Board of Regents, the budget for 1941 has been adopted, calling for an estimated income of \$111,700 00 and estimated expenditures of \$87,276 50 Respectfully submitted by William D Stroud, Treasurer"

Mr E R Loveland, as Executive Secretary, presented the following report

"The Executive Secretary's report is supplementary to the reports of the Treasurer and Secretary General Much that has happened in the College has also been referred to in the address of your President

"The past year again has been characterized by an extension of activities of the College and in the duties of the Executive Offices, but at the same time our work has been rendered more interesting by its diversity We have had at all times the co-operation and kindly aid of all the Officers, Regents and Governors I should like especially to pay tribute to the members of the various College Committees that have

made such a contribution during the past year. Members at large have little opportunity to know how much time and effort these men devote to our organization.

"During the past year the volume basis of the "Annals of Internal Medicine" has been changed so that instead of one volume of twelve issues per year, we are publishing, for the sake of convenience of indexing and filing, two volumes each of six issues. A completely new and revised Directory of the College was published last Autumn and distributed to all members. Earlier in 1941, 1800 copies of the College History were reprinted so that there will be an adequate supply to furnish a copy to every new member entering the College. There have been numerous Regional Meetings conducted by College Governors for their particular states or regions, as a result of which there has been an increased participation by our members in College affairs. These meetings contribute greatly to a better understanding of the objectives and activities of your organization, and they will be of even greater importance in extending and cementing together the interests of our members in these times when attendance at the Annual Sessions may become more difficult.

"The work of preparing for this meeting has been lightened by the ready assistance and cooperation of President Lee, General Chairman Lepak and his efficient local committees. The registration totals 1848, of whom 162 are visiting women. Although these are not all members of the College, the great majority are.

"We know of no other national medical society that actually has as large a percentage of its members in attendance at its annual meetings as this College.

"We are always happy to welcome our members at the College Headquarters in Philadelphia. It is our desire to be of service to each one of you whenever and in whatever way it is possible. By all means, in these times, give your complete support and interest to our American Institutions, and especially I speak for the College. Our American Countries and England are the last outposts of such institutions as this College. In Continental Europe, all such organizations have been buried with their martyrs, and it behooves us to proceed with ever increasing zeal to preserve these societies through this war, else there will be no chance to return to the so-called 'American way of life' when this war is over."

The Secretary General, Dr. George Morris Piersol, presented the following report:

"Membership—Since the last Annual Session of the College we have lost by death 48 Fellows, 5 Associates, or a total of 53, by resignation, 3 Fellows, 11 Associates, total 14, by failure to qualify for advancement to Fellowship within the maximum five-year period prescribed by the By-Laws, 17 Associates, by delinquency 7 Fellows and 2 Associates, total 9. The total membership mortality for the past year has been 93. There have been elected to Fellowship 302 physicians, only a few of whom were elected directly to Fellowship because of special qualifications and outstanding accomplishments. There have been elected to Associateship 220, 1 Fellow has been reinstated and 1 Fellow dropped from the roster because his whereabouts no longer can be determined. The total membership of the College as constituted is as follows:

4 Masters
3,728 Fellows
1,106 Associates
<hr/>
4,838 TOTAL

'Life Membership—16 Fellows have become Life Members during the past year making a grand total of 183, of whom 17 are deceased, leaving 166 on the roll at this time.

"The Advisory Committee on Postgraduate Courses, with the whole-hearted cooperation of our officers, Regents and Governors, and many of our Fellows, has

conducted a series of Postgraduate Courses, some during February and some as premeeting courses. Eleven such courses were scheduled, but owing to conditions of war and other influences, 5 of these courses were cancelled, but the others were highly successful and well attended with a registration equivalent to that of the preceding year, even though some of our current courses were withdrawn. The College will continue this important work, and the schedule of courses for 1942-43 will be initially announced in the near future. The Advisory Committee on Postgraduate Courses during the past year has also initiated series of Postgraduate Lectures known as 'Postgraduate Nights,' for Medical Officers at one of the large naval hospitals in the East, and it is anticipated that this program will be extended to the larger base hospitals and naval hospitals in other parts of the country.

"Three additional research Fellowships have been awarded by the College to begin this coming summer or autumn."

Dr Piersol, turning to President Lee and presenting him with an engraved, silver feruled gavel, said

"Mr President, during the past year while you have so ably and wisely guided the destinies of this College you have become more than ever endeared to all who have had the privilege of working with you. We are deeply appreciative of the never-failing spirit of cooperation and courtesy that has marked all our association. Therefore, on behalf of the Officers, Regents and Governors of the American College of Physicians, I have the honor to present you with this Gavel, an enduring symbol of the high office you have held, as well as a token of our affection and esteem."

President Lee "Thank you, Mr Secretary General. It is with peculiar pleasure that I use this gavel for the first time in inducting the President-Elect, Dr James E Paullin, into the office of President."

Dr Paullin, assuming the chair "Dr Lee, members of the College, ladies and gentlemen. To say that I am not deeply sensitive and appreciative beyond a mere expression of words of the honor which you have conferred upon me by elevating me to this, the highest office to be given by this Association, is but a feeble method of telling you the emotion that I feel at this time.

"When you made me President-Elect of this organization one year ago, the country was not facing the situation it now does. Things have changed, but with it there has been the growing interest and devotion of the members of the College to the purpose of National Defense.

"I again pledge my allegiance to the College and its membership, to do the best that I possibly can for the furtherance of that one objective which is foremost in the minds and hearts of every true, loyal American—the winning of this war and the preservation of the democratic thoughts and democratic ideals and the very things for which your forefathers and mine fought, bled and died. That now, is our job. Whatever it takes to accomplish that, you are willing, I am willing, all of us are willing to do.

"To that end I now pledge myself to you and you to me, so that it is unanimous."

President Paullin called for the report of the Committee on Nominations. Dr Edward L Bortz, Chairman of the Committee, presented the names of nominees for the elective offices, the Board of Regents and the Board of Governors. President Paullin acted upon each group individually and asked for nominations from the floor in accordance with provisions of the By-Laws. There were no nominations from the floor. Nominations for the various offices, by resolution regularly adopted, were closed and the nominees were elected by acclamation. (The names of the individuals so elected are published elsewhere in this issue of the ANNALS.)

President Paullin requested Colonel Hugh Morgan and Dr Gorham Brigham to escort the President-Elect, Dr Ernest E Irons, to the rostrum. This was done amid applause from the audience.

DR IRONS "I am deeply appreciative of this signal honor, and especially so when I read the list of my distinguished predecessors. And as Dr Paullin has noted, we are in the midst of a war—a war that we must win and shall win.

"In addition to pledging you my present efforts for the College, I also pledge that I shall do everything in my power to assist in the winning of this war. Thank you."

On motion by Dr Thomas T Holt, seconded by many, and carried by a unanimous rising vote, the following resolutions were adopted:

"BE IT RESOLVED, that the cordial and sincere thanks of the entire membership of the American College of Physicians be extended to our retiring President, Dr Roger I Lee, to the General Chairman, Dr John Lepak, to the new President, Dr James E Paullin, to the chairmen and members of the St Paul committees, individually and collectively, to Mrs Edward Goltz and her efficient Committee on Ladies' Entertainment, for their faithful and courteous work in the conduct of this memorable Session, and

"BE IT FURTHER RESOLVED, that our appreciation be extended also to those cooperating agencies and the University of Minnesota Medical School, the hospitals, the public press, the Ramsey County Medical Society, Mr Julius Perl and the St Paul Association of Commerce, and the management and staff of the Hotel Lowry and the Hotel St Paul for their cooperation and help, all of which has contributed so much to our entertainment, pleasure and comfort."

There being no further business the meeting adjourned.

E R LOVELAND,
Executive Secretary

NEW ELECTIONS OF OFFICERS, REGENTS AND GOVERNORS

At the Annual Business Meeting of the American College of Physicians, Thursday, April 23, 1942, in St Paul, Minn., the following were elected:

Officers

<i>President-Elect</i>	Ernest E Irons, Chicago, Ill
<i>First Vice-President</i>	Charles H Cocke, Asheville, N C
<i>Second Vice-President</i>	Henry R Carstens, Detroit, Mich
<i>Third Vice-President</i>	A Comingo Griffith, Kansas City, Mo

Regents

Term Expiring 1945

Francis G Blake, New Haven, Conn
James F Churchill, San Diego, Calif
Reginald Fitz, Boston, Mass
Roger I Lee, Boston, Mass
Charles T Stone, Galveston, Tex

Governors

Term Expiring 1943

Robert O Brown, Santa Fe NEW MEXICO

Term Expiring 1941

Gilbert M Stevenson Ancon REPUBLIC OF PANAMA and the
CANAL ZONE

Term Expiring 1945

Olive C Melson, Little Rock	ARKANSAS
Ernest H Falconer, San Francisco	CALIFORNIA (Northern)
Benjamin F Wolverton, Cedar Rapids	IOWA
Edgar Hull, New Orleans	LOUISIANA
Douglas Donald, Detroit	MICHIGAN
Edgar V Allen, Rochester	MINNESOTA
Ralph Kinsella, St Louis	MISSOURI
Lawrence Parsons, Reno	NEVADA
Harry T French, Hanover	NEW HAMPSHIRE
George H Lathrope, Newark	NEW JERSEY
Paul F Whitaker, Kinston	NORTH CAROLINA
Julius O Anson, Bismarck	NORTH DAKOTA
Alexander M Burgess, Providence	RHODE ISLAND
Kenneth M Lynch, Charleston	SOUTH CAROLINA
Paul K French, Burlington	VERMONT
Walter B Martin, Norfolk	VIRGINIA
Charles E Watts, Seattle	WASHINGTON
Albert H Hoge, Bluefield	WEST VIRGINIA
Hugh A Farris, St John	MARITIME PROVINCES
Charles F Moffatt, Montreal	QUEBEC

At a meeting of the Board of Governors, Wednesday, April 22, 1942, Dr William B Breed, Boston, Mass, was elected Chairman of the Board of Governors of the College Dr C W Dowden, Louisville, Ky, is Vice Chairman

ELECTIONS TO MEMBERSHIP, ST PAUL, APRIL 19, 1942

Elections to Fellowship

Ralph Irving Alford, Montclair, N J

Walter Hilmar Baer, Manteno, Ill
 Samuel Perkins Bailey, Brooklyn, N Y
 Lyle Andrew Baker, Hines, Ill
 James Ian Baltz, Detroit Mich
 Wendell Hugh Bennett, Youngstown, Ohio
 Clifford Albert Best, (MC), U S Army
 Henry Grady Bevil, Beaumont, Tex
 Samuel Blinder, New York, N Y
 Edmund Clyde Boots, Pittsburgh, Pa
 Charles Arthur Breck, Wallingford, Conn
 Maurice Bruger, New York, N Y
 George Nelson Burger, Covington, Ky

Joseph Bishop Cady, Lebanon, Pa
 Eugene Calvelli, Port Washington, N Y
 George Daniel Capaccio, Seattle, Wash
 John William Cass, Jr, Brookline, Mass
 Franklin Chester Cassidy, Fort Bayard, N M
 Edwin Gurney Clark, Baltimore, Md
 Paul Chester Clark, Syracuse, N Y

Hunt Cleveland, Anniston, Ala
 James W Colella, Johnson City, N Y
 Thomas Bartholomew Cunnane, Los Angeles, Calif
 John DePaul Currence, New York, N Y
 Hayden Harrison Cutler, Houston, Tex

Earl Alfred Daugherty, Philadelphia, Pa
 John Arthur Daugherty, Harrisburg, Pa
 Boni James DeLaureal, New Orleans, La
 Preston Vine Dilts, Pittsfield, Ill
 Samuel Donner, Hartford, Conn
 Ralph Lafayette Drake, Wichita, Kans
 Morris Lionel Diazin, Jackson Heights, L I, N Y

Franklin Gessford Ebaugh, Denver, Colo
 Benjamin Madison Eis, Brooklyn, N Y
 Stanley Howard Erlenback, Rochester, N Y
 Clayton Bernard Ethridge, Washington, D C
 George Francis Evans, Clarksburg, W Va
 James Bryan Eyerly, Chicago, Ill

Theodore Richard Failmezger, Madison, N J
 Carlos Eugene Fallon, Newburgh, N Y
 Orin Jocevious Farness, Tucson, Ariz
 Robert Hanna Felix, U S P H S, Baltimore, Md
 David Irving Fertig, Hartsdale, N Y
 Edgar Minton Fetter, San Diego, Calif
 James William Finch, Hobart, Okla
 Marion Stevenson Fitchett, Norfolk, Va
 Maurice Patrick Foley, Los Angeles, Calif
 Silas Crume Fulmer, Little Rock, Ark
 Joseph John Furlong, Milwaukee, Wis

Lawrence Bernard Gang, Huntington, W Va
 Thomas Cresson Garrett, Philadelphia, Pa
 Edwin Wilder Gates, Niagara Falls, N Y
 Fred A J Geier, Washington, D C
 William Roland Gibson, Los Angeles, Calif
 Olin Burr Gober, Temple, Tex
 Benjamin Elmer Goodrich, Dearborn, Mich
 Murray Eugene Goodrich, Toledo, Ohio
 Robert William Gordon, Denver, Colo
 Randolph Bryan Grinnan, Jr, Norfolk, Va
 Herman Petrus Gunnar, Chicago, Ill

William Richard Hallaran, Cleveland, Ohio
 George Clifford Hamilton, Binghamton, N Y
 Paul Victor Hamilton, Cincinnati, Ohio
 Maurice A F Hardgrove, Milwaukee, Wis
 Tinsley Randolph Harrison, Winston-Salem, N C
 Reid Russell Heffner, New Rochelle, N Y
 Leon Hughes Hetherington, Pittsburgh, Pa
 William Roy Hewitt, Tucson, Ariz

Ford Kimmel Hick, Oak Park, Ill
 Donald Frederick Hill, Tucson, Ariz
 Horton Corwin Hinshaw, Rochester, Minn
 Ralph Howard Homan, El Paso, Tex
 John Harlan Hornbaker, Hagerstown, Md
 Ralph Charles Hoyt, Reading, Pa
 Emory G Hyatt, Tulsa, Okla

Harold Joseph Jeghers, Boston, Mass
 Joseph Francis Jenovese, Hartford, Conn
 Walter Steen Jensen, (MC), U S Army
 William Michael Jermain, Milwaukee, Wis
 Edward Morgan Jones, Endicott, N Y
 Robert Harold Jones, Fairmont, W Va
 Leonard Francis Jourdonais, Evanston, Ill

Louis Nelson Katz, Chicago, Ill
 Samuel Russel Kaufman, Wilkes-Barre, Pa
 Marion Reginald King, U S P H S, Springfield, Mo
 Otis Gardner King, Bluefield, W Va
 Estelle Elizabeth Kleiber, New Brunswick, N J
 Charles John Koerth, San Antonio, Tex
 Joseph Rudolph Kriz, Toledo, Ohio

Leo Frederick La Palm, Rochester, N Y
 Albert Theodore Leatherbarrow, Hampton Station, N B
 Edward Paul Leeper, Dallas, Tex
 Seaborn Joseph Lewis, Beaumont, Tex
 James J Lightbody, Detroit, Mich

Chauncey Carter Maher, Chicago, Ill
 Tim Joseph Manson, Chattanooga, Tenn
 Frank Baker Marsh, Salisbury, N C
 Frederick Eugene Marsh, Chattanooga, Tenn
 Ernest George McEwen, Evanston, Ill
 Robert McGrath, New York, N Y
 Floyd Thomas McIntire, San Angelo, Tex
 Frank Meyers, Buffalo, N Y
 Fred Nathan Miller, Eugene, Ore
 Ralph Bretney Miller, Boston, Mass
 Lester M Morrison, Philadelphia, Pa
 Emma Sadler Moss, New Orleans, La
 William Peter Mull, (MC), U S Navy
 Wendell Stanley Muncie, Baltimore, Md

John Noll, Jr, Youngstown, Ohio
 Thomas Ochsner Nuzum, Janesville, Wis

Arthur Martin Olsen, Rochester, Minn

Henry Felch Page, Philadelphia, Pa
 Robert Clinton Page, Mount Vernon, N Y
 Franklin Bruce Peck, Indianapolis, Ind

George Peter Perakos, New Britain, Conn
 William Harvey Perkins, Philadelphia, Pa
 Elbert Lapsley Persons, Durham, N C
 Aaron Robert Peskin, New York, N Y
 Helen Sinclair Pittman, Boston, Mass
 Harry William Pimakov, Baltimore, Md

Harold Lawrence Rakov, Kingston, N Y
 Edward Conrad Reifstein, Jr, Syracuse, N Y
 Murray Lambert Rich, Covington, Ky
 Isidore Leon Robbins, New Orleans, La
 Donald Herbert Root, Quincy, Ill
 Abraham Rudy, Boston, Mass
 Nelson G Russell, Jr, Buffalo, N Y

Oscar Adam Sander, Milwaukee, Wis
 John Albert Schindler, Monroe, Wis
 Curt Paul Schneider, Detroit, Mich
 Otis B Schreuder, (MC), U S Army
 John William Scott, Edmonton, Alta
 Grady Oscar Segrest, Mobile, Ala
 Joseph Haskell Shaffer, Detroit, Mich
 William Woolf Shapiro, Chicago, Ill
 John Charles Sharpe, Omaha, Nebr
 Joseph Dunbar Shields, Jr, Concord, N H
 Donald Sanford Smith, Pontiac, Mich
 Opie Norris Smith, Greensboro, N C
 William Andrew Somerville, New York, N Y
 Clair Grove Spangler, Reading, Pa
 Wesley William Spink, Minneapolis, Minn
 Aaron Alfred Sprong, Sterling, Kan
 Harold Jones Starr, Chattanooga, Tenn
 Alfred Stengel, Jr, Philadelphia, Pa
 Ralph Eugene Swope, New York, N Y

Samuel Gale Taylor, III, Chicago, Ill
 Harry Burger Thomas, York, Pa
 Harry Edward Thompson, Tucson, Ariz
 Richard Carmichael Tilghman, Baltimore, Md
 Warren Irving Titus, Glen Cove, L I, N Y

Howard Wakefield, Chicago, Ill
 Frank Bolles Wakeman, (MC), U S Army
 Albert Wicken Wallace, Miami Beach, Fla
 Robert Pulley Wallace, New York, N Y
 James Alexander Walsh, Peoria, Ill
 Albert Gayden Ward, Jackson, Miss
 Richard Nathaniel Washburn, Rensselaer, Ind
 Walter Weissenborn, Hartford, Conn
 Merritt Bryant Whitten, Dallas, Tex
 William Lewis Winters, Highland Park, Ill
 Francis Roman Wise, York, Pa
 Sidney Elmer Wolpaw, Cleveland, Ohio

Lawrence Foss Woolley, Towson, Md

Frederick Otto Zillesen, Easton, Pa

Elections to Associateship

Harold Herbert Aaron, New York, N Y

Carl Richard Ahroon, Jr, Bloomington, Ill

Charles Henry Armentrout, Asheville, N C

Philip Klaus Arzt, Jamestown, N D

Gerald Seler Backenstoe, Emmaus, Pa

Roland Wellington Banks, Yeadon, Pa

Duncan William James Bell, Providence, R I

Maxwell Rufus Berry, Jr, Richmond, Va

Earl Julius Bieri, Hot Springs National Park, Ark

Samuel Blackwell, Memphis, Tenn

William Cooper Buschemeyer, Louisville, Ky

Benjamin Burroughs Bushong, Traverse City, Mich

Donald Clarence Campbell, Rochester, Minn

Eugene Charles Chamberlain, Fort Lauderdale, Fla

Donald Tillinghast Chamberlin, Boston, Mass

Herman Maurice Chesluk, Detroit, Mich

William Godfrey Childress, Valhalla, N Y

Abraham George Cohen, New York, N Y

Samuel James Cohen, Brooklyn, N Y

James Stuart Daly, Trail, B C

William Hill Dearing, Rochester, Minn

Rurico Santiago Diaz Rivera, San Juan, P R

William Clay Dine, Jr, Amarillo, Tex

Henry Dolger, New York, N Y

Charles William Dowden, Louisville, Ky

Harold Raymond Drysdale, Rochester, N Y

Samuel Lawrence Ellenberg, New York, N Y

Hugo Tristram Engelhardt, New Orleans, La

John Paul English, Rochester, Minn

James Brookbank Fisher, Wichita, Kan

Ralph Gibson Fleming, Durham, N C

Harry Thomas Foley, II, Pittsburgh, Pa

Roberto Francisco Azize, Arecibo, P R

William Robert Galbreath, Jr, New Orleans, La

Russell Arthur Garman, Jeannette, Pa

Samuel M Gingold, Detroit, Mich

Eddie Monroe Gordon, Jr, U S P H S, Mobile, Ala

Richard Sigmund Gubner, Brooklyn, N Y

James Whitney Hall, Jr, Chicago, Ill

William Marion Hall, Shreveport, La

Ralph Orville Hayden, St Charles, Mo

George Anthony Hellmuth, Chicago, Ill
 Thomas Robert Hepler, Harrisburg, Pa
 Howard Eugene Heyer, Chicago, Ill
 Robert Emmett Hobbs, Shenandoah, Pa
 Harold Jennings Hoxie, Los Angeles, Calif

William Knowlton Ishmael, Oklahoma City, Okla

George Miller Jones, Ann Arbor, Mich

Mennasch Kalkstein, New York, N Y
 Solomon Salkind Kauvar, Denver, Colo
 Paul Edmund Keller, (MC), U S Army
 Richard James Kihullen, Wilkes-Barre, Pa
 Laurance Wilkie Kinsell, East Stroudsburg, Pa
 Jack D Kirshbaum, Chicago, Ill
 Solomon Krell, New York, N Y
 Maurice Alexander Kugel, Miami Beach, Fla
 Franklin Arthur Kyser, Galesburg, Ill

Edwin Lever Lame, Philadelphia, Pa
 Clarence Watson LeDoux, Baltimore, Md
 Howard James Lee, Oshkosh, Wis
 Harry D Leinoff, New York, N Y
 Bernard Isaac Lidman, Norfolk, Va
 David Frank Loewen, Decatur, Ill
 Alexander Leon Louria, Brooklyn, N Y

William David Mackay, Mount Vernon, N Y
 John Edward Manley, Scranton, Pa
 Donald Feige Marion, Detroit, Mich
 Ralf Martin, Portland, Maine
 Robert Archibald Matthews, Philadelphia, Pa
 Milton John Matzner, Brooklyn, N Y
 Thomas Crooke McCleave, Jr, Oakland, Calif
 George Gordon McHardy, New Orleans, La
 Christopher John McLoughlin, Rochester, Minn
 Robert Lindsay McMillan, Winston-Salem, N C
 Ronald John McNamara, Charleston, W Va
 Leo Joseph Meienberg, Portland, Ore
 Paul Reims Meyer, Port Arthur, Tex.
 Raymond Everett Miller, New York, N Y
 Lawrence T Minish, Jr, Louisville, Ky
 William John Mitchell, Los Angeles, Calif
 Martin Alvin Murphy, Brooklyn, N Y

Edward Stewart Orgain, Durham, N C

James Earl Patterson, Buffalo, N Y
 Horace Pettit, Philadelphia, Pa
 Harry Harvey Pote, Philadelphia, Pa

Ieland Paul Ralph, Grand Rapids, Mich
 Henry Rascoft, Brooklyn, N Y

Richard Reeser, Jr, Daytona Beach, Fla
 Max Harry Rosenblum, Steubenville, Ohio
 Abraham Isaac Rosenstein, New York, N Y
 Chauncey Lake Royster, Raleigh, N C
 Henry Irving Russek, U S P H S, Brooklyn, N Y

Martin Schaeffer, Detroit, Mich
 Eugene Mathias Schloss, Philadelphia, Pa
 George Schwartz, New York, N Y
 Lamont R Schweiger, Shorewood, Wis
 Maurice McLaurin Scurry, Ann Arbor, Mich
 Louis Bernard Shapiro, Manteno, Ill
 Edward David Sherman, Sydney, N S
 Seymour Harry Silvers, Brooklyn, N Y
 Alfred Harvey Simmons, Harrisburg, Pa
 Howard Nelson Simpson, Springfield, Mass
 Ben Slutzky, Omaha, Neb
 Kendrick Adelbert Smith, Rochester Minn
 Lucian Anderson Smith, Rochester, Minn
 Wilbur Anderson Smith, New York, N Y
 Charles Keith Stuart, London, Ont
 Stanley Richard Szymanski, Livingston, N Y

Henry Allen Tadgell, Boston, Mass
 William Garland Talmage, Succasunna, N J
 Arthur Martin Tiber, New York, N Y
 James Eugene Toups, New Orleans, La

Frank Carl Val Dez, Chicago, Ill
 Aloysius Vass, Springfield, Ill
 Walter Lyle Voegtlin, Seattle, Wash
 Earl Stanley Vollmer, Glenside, Pa

Leon Hugh Warren, Washington, D C
 Alton Floyd Williams, Fort Jackson, S C
 William Hays Windley, New Orleans, La

Ellis William Young, Pittsburgh, Pa

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

The following Boards have announced schedules of their examinations as follows

AMERICAN BOARD OF INTERNAL MEDICINE William S Middleton, M D, Secretary 1301 University Ave Madison, Wis	<i>Written Examinations</i> October 19, 1942, applications for admission must be filed before September 1, 1942
	<i>Oral Examinations</i> Philadelphia, Pa, June, 1942, in advance of the meet- ing of the American Medical As- sociation in Atlantic City, N J

AMERICAN BOARD OF DERMATOLOGY AND
SYPHILOLOGY
C Guy Lane, M D, Secretary
416 Marlboro St
Boston, Mass

Written Examinations Will be given
in various centers November 16,
1942, applications for admission
must be filed before October 6,
1942

Oral Examinations Cleveland, Ohio,
January 14-15, 1943, applications
for admission must be filed before
December 8, 1942

AMERICAN BOARD OF PEDIATRICS
C A Aldrich, M D, Secretary
707 Fullerton Ave
Chicago, Ill

Written Examinations Locally Sep-
tember 18, 1942

Oral Examinations Chicago, Ill, No-
vember 2-3, 1942, in advance of
the meeting of the American Aca-
demy of Pediatrics, applications
for admission must be filed before
July 1, 1942

AMERICAN BOARD OF PSYCHIATRY AND NEU-
ROLOGY
Walter Freeman, M D, Secretary
1028 Connecticut Ave, N W
Washington, D C

Written Examinations New York, N
Y, December, 1942, applications
for admission must be filed before
October 1, 1942

AMERICAN BOARD OF RADIOLOGY
B R Kirklin, M D, Secretary
Mayo Clinic
Rochester, Minn

Oral Examinations Atlantic City, N
J, June 4-6, 1942, November,
1942 (date and place not yet
selected)

For further details and application forms communicate with the respective secre-
taries

REGIONAL MEETING OF FLORIDA MEMBERS

The Florida Chapter of the American College of Physicians held its Annual
Regional Meeting in Hollywood, Florida, on April 13 The program was as follows

- 1 "Clinical Management of Hodgkin's Disease"
 - (a) Clinical Viewpoint
W Wellington George, F A C P, West Palm Beach
 - (b) Radiological Viewpoint
F K Herpel, F A C P, West Palm Beach
- 2 "X-Radiation in the Treatment of Pituitary Basophilism"
George R Crisler (Associate), Winter Park
- 3 "Gastrointestinal Lesions Simulating Angina Pectoris"
Paul B Welch, F A C P, Miami
- 4 "Resumé on Nephrosis in Childhood"
J Sudler Hood (Associate), Clearwater

The Chapter voted unanimously and the secretary was instructed to communicate
with the College Governor for Georgia, recommending that the College be invited
to hold its 1943 Annual Session in Atlanta, Georgia, the general feeling being that
this would be a proper tribute to the incoming President, Dr James E Paullin, of
Atlanta

The Chapter also voted unanimously to recommend through its Governor, Dr T Z Cason, that the Board of Regents consider holding the Annual Session of the College either at a later date in the spring or at an early date in the autumn. This action was recommended because of the difficulty Florida members experience in attending the Sessions since these convene at a time when doctors in territories dependent upon the tourist season are unable to leave their practices. When the College some years ago changed the date of its Annual Sessions from February to April, these physicians were helped considerably for some two years, but the tourist season in the south has changed, fluctuating from the later winter through early spring. The Florida Chapter felt that many southern states depend upon business from winter tourists and that many others, besides those from Florida, are handicapped by holding the Meeting in early April.

GIfts TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following reprints of publications by members of the College

Dr Benjamin R Allison F A C P, Hewlett N Y—1 reprint,
 Dr Louis H Bauer, F A C P, Hempstead, N Y—4 reprints,
 Dr J Edward Berk (Associate), Philadelphia Pa—2 reprints
 Dr Leon L Blum (Associate), Terre Haute, Ind—1 reprint
 Dr Eugene P Campbell (Associate), Philadelphia, Pa—11 reprints,
 Dr Lyman B Carruthers, F A C P Miraj, S M C India—2 reprints
 Dr Darrell C Crain Jr (Associate), Washington, D C—1 reprint
 Dr Irving Greenfield (Associate), Brooklyn, N Y—2 reprints,
 Dr George F Harsh (Associate), San Diego, Calif—5 reprints
 Dr Oswald F Hedley, U S P H S Bethesda, Md—1 reprint,
 Dr Arthur A Herold F A C P, Shreveport, La—4 reprints,
 Dr Earl Jones, F A C P, Alexandria La—1 reprint,
 Oza J LaBarge, F A C P Major (MRC) U S Army—1 reprint,
 Dr Evans W Pernokis (Associate), Chicago, Ill—1 reprint
 Dr Max Pinner F A C P New York, N Y—2 reprints,
 Dr Samuel G Plice, F A C P, Chicago, Ill—1 reprint
 Dr William T Ramey F A C P, Fayetteville N C—1 reprint,
 Dr William B Rawls, F A C P, New York, N Y—1 reprint,
 Dr Martin E Rehfuess, F A C P Ardmore, Pa—2 reprints
 Dr Nathaniel E Reich (Associate), Brooklyn N Y—4 reprints,
 Dr Horace K Richardson, F A C P, Baltimore Md—1 reprint,
 Dr Rafael Rodriguez-Molina, F A C P, San Juan P R—1 reprint,
 Dr Albert H Rowe, F A C P, Oakland, Calif—2 reprints,
 Dr Leon Schiff, F A C P Cincinnati Ohio—2 reprints,
 Dr Jacob J Singer, F A C P, Los Angeles, Calif—2 reprints,
 Dr Lester D Watson (Associate), Milton, Mass—2 reprints

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College.

Dr Reuben Finkelstein, Brooklyn, N Y
 Dr Arthur A Herold, Shreveport, La

Under the Presidency of Dr Herman O Mosenthal, F A C P , New York, N Y , the American Diabetes Association will hold its 2nd Annual Meeting in Atlantic City, N J , on June 7, 1942 The annual business meeting will be held during the morning and will be followed by the Presidential Address After this address there will be a round table discussion with Dr Mosenthal acting as Chairman, and Dr Joseph H Barach, F A C P , Pittsburgh, Pa , Dr Edward S Dillon, F A C P , Philadelphia, Pa , and Dr Elliott P Joslin, F A C P , Boston, Mass , participating During the afternoon scientific session the following members of the College will present papers

Dr Franklin B Peck, F A C P , Indianapolis, Ind—"Action of Insulin",

Dr Joseph T Beardwood, Jr, F A C P , Philadelphia, Pa—"The Diabetic in the Defense Program",

Dr Eaton M MacKay, F A C P , La Jolla, Calif—"Acidosis"

Dr Roger I Lee, F A C P , Boston, Mass , was recently made an honorary Fellow of the Royal College of Physicians of England

Dr Ralph Pemberton, F A C P , Philadelphia, Pa , addressed the Buffalo Academy of Medicine at Buffalo, N Y , April 8, 1942, on "Pathology and Rational Therapy of Chronic Arthritis" On April 23, 1942, Dr Pemberton delivered an address before the students of the Long Island College of Medicine, Brooklyn, N Y

Dr Seeley G Mudd, F A C P , Pasadena, Calif , has been appointed Dean of the University of Southern California School of Medicine, Los Angeles

Dr Lester Neuman, F A C P , Washington, D C , addressed the New Castle County Medical Society in Wilmington, Del , January 20, 1942 Dr Neuman spoke on "New Horizons in Clinical Pathology"

Dr George H Gehrman, F A C P , Wilmington, Del , was elected one of the Vice Presidents of the Delaware Public Health Association, at a recent meeting

On March 20, 1942, Dr Arthur C Christie, F A C P , Washington, D C , addressed the Northwest Branch of the Chicago Medical Society The subject of Dr Christie's address was "What Is Being Done to Control Cancer"

Among the speakers at the meeting of the Central Neuropsychiatric Hospital Association in Des Moines, Iowa, March 19-20, 1942, were:

Dr George T Harding, III, F A C P , Columbus, Ohio—"Acute Problems Facing the Private Psychiatric Hospital";

Dr Titus H Harris, F A C P , Galveston, Tex—"Psychiatry and the National Emergency".

Dr William C Menninger, F A C P , Topeka, Kan—"Morale and the Private Psychiatric Hospital"

The Medical Society of the State of New York recently sponsored a postgraduate course on "Arteriosclerosis and Aging" for the Jefferson County (N Y) Medical Society Among those who conducted the course were

April 23 1942, Dr S Bernard Wortis, F A C P, New York, N Y—"Neuro-psychiatric Aspects Diagnosis and Treatment",

May 14, 1942, Dr William Goldring, F A C P, New York, N Y—"Renal and Cardiac Aspects, Diagnosis and Treatment".

May 21, 1942 Dr Irving S Wight, F A C P, New York, N Y—"Peripheral Vascular Aspects Diagnosis and Treatment"

On April 2, 1942, Dr James S McLester, F A C P, Birmingham, Ala, Professor of Medicine, University of Alabama School of Medicine, delivered the Hermann M Biggs Memorial Lecture at the New York Academy of Medicine Dr McLester spoke on "Nutrition and the Nation at War"

Dr Frederick W Williams (Associate), New York, N Y, was one of the speakers at a symposium on "Reduction in Mortality Due to Gangrene in the Diabetic," at a recent clinical meeting of the New York Diabetes Association

Dr John G Mateer, F A C P, Detroit, Mich, spoke on "Comparative Sensitivity and Reliability of the Newer Liver Function Tests and Their Relationship to Medical and Surgical Problems" at a meeting of the Academy of Medicine, of Cincinnati, Ohio, February 17, 1942

Dr R Lomax Wells F A C P, Washington, D C, has been elected Chairman of the Interprofessional Conference, a new organization sponsored by the Medical Society of the District of Columbia to discuss the mutual problems of the pharmaceutical, dental and nursing professions

The Midwestern Section of the American Congress of Physical Therapy held its spring session April 6, 1942, in Iowa City, Iowa At this meeting Dr Max K Newman (Associate), Detroit, Mich, spoke on "Hypothermic Anesthesia in Extremity Surgery," and Dr Frank H Krusen, F A C P, Rochester, Minn, spoke on "The Relation of Physical Therapy in War"

The Iowa State Medical Society held its 91st Annual Session in Des Moines, Iowa, April 15-17, 1942 Among the guest speakers were

Dr John A Toomey, F A C P, Cleveland, Ohio—"Differential Diagnosis of Meningeal Irritations",

Dr Reginald Fitz, F A C P, Boston, Mass—"Certain Peculiarities of Gallstone Disease"

Dr Edward B Krumbhaar, F A C P, Philadelphia, Pa, delivered a public lecture sponsored by the College of Physicians of Philadelphia, on "Superstition and Medical Progress"

The Mary Scott Newbold Lecture of the College of Physicians of Philadelphia was delivered on May 6, 1942, by Dr C Sidney Burwell, F A C P, Boston, Mass The subject of Dr Burwell's lecture was "Studies of the Circulation in Congenital Affections of the Heart and Their Application to Some of the Problems of Heart Disease"

The Philadelphia County Medical Society held its 7th Annual Postgraduate Institute in Philadelphia, April 13-17, 1942. Among the local speakers at this Symposium on Modern Therapy were.

Dr T Grier Miller, F A C P—"The Significance of Nutrition in Relation to National Defense",

Dr G Harlan Wells, F A C P—"Diabetes Complicated by Tuberculosis",

Dr Charles C Wolferth, F A C P—"The Management of Coronary Disease in the Diabetic",

Dr Harrison F Flippin, F A C P—"Recent Advances in Sulfonamide Therapy",

Dr William G Leaman, Jr, F A C P—"The Management of the Cardiovascular Complications of Anemia and the Deficiency Diseases",

Dr Ralph Pemberton, F A C P—"Effective Organization of the Treatment of Arthritis"

At the meeting of the Tri-State Medical Association of the Carolinas and Virginia in Greenville, N C, February 23-24, 1942, Dr George R Wilkinson (Associate), Greenville, was installed as President and Dr Walter B Martin, F A C P, Norfolk, Va, was named a Vice President

The American Association of Pathologists and Bacteriologists held its 42nd Annual Meeting in St Louis, Mo, April 2-3, 1942. Among the speakers were

Dr Carl V Weller, F A C P, Ann Arbor, Mich—"Statistical Investigation of the Correlation Between Mastopathia Cystica and Mammary Cancer",

Dr Jacob Werne, F A C P, Jamaica, N Y—"Postmortem Evidence of Acute Infection in Unexpected Death of Infancy and Childhood",

Dr Howard T Karsner, F A C P, Cleveland, Ohio—"General Considerations of Functioning Tumors of Endocrine Glands",

Dr Ernest M Hall, F A C P, Los Angeles, Calif—"The Incidence of Rheumatic Stigmas in Nonrheumatic Hearts"

Dr Logan Clendenning, F A C P, Kansas City, Mo, spoke on "The Place of Obstetrics in the Various Epochs of the History of Mankind," and Dr Alexander E Brown, F A C P, Rochester, Minn, spoke on "History and Pharmacologic Aspects of Chemotherapeutic Drugs," at the 2nd American Congress on Obstetrics and Gynecology held in St Louis, Mo, April 6-10, 1942

The American Society for Pharmacology and Experimental Therapeutics held its annual meeting in Boston, Mass, March 31-April 4, 1942. During a symposium on "Morphine Problems," Dr Harold G Wolff, F A C P, New York, N Y, spoke on "Pain and Its Relief by Morphine and Related Substances," and Dr Clifton K Himmelsbach (Associate), Lexington, Ky, spoke on "Present Status of Morphine Addiction Studies", during a symposium on "Deficiency Diseases," Dr Norman H Jolliffe, F A C P, New York, N Y, presented a paper on "Vitamins in the Practice of Medicine," and Dr William H Sebrell, Jr, F A C P, Washington, D C, presented a paper on "Vitamins in Public Health"

The 69th Annual Meeting of the Florida Medical Association was held in Hollywood, Fla, April 13-15, 1942. Among the speakers were.

Dr James A Bradley, F A C P St Petersburg, Fla—"Bed Rest in Coronary Thrombosis",

Dr Warren W Quillian F A C P Coral Gables, Fla—"Pyurias in Childhood Their Significance and Treatment"

Dr William C MacCarty, F A C P, and Dr Byrl R Kirklin, F A C P, both of Rochester, Minn spoke on "Radiologic and Pathologic Studies of Prepyloric Ulcer," at the spring meeting of the Minnesota Radiological Society held in Rochester, March 28, 1942

Among the speakers at the annual session of the Missouri State Medical Association held in Kansas City Mo, April 27-29, 1942, were

Dr Karl W Brimmer, F A C P, Washington, D C—"Faith, Hope and Cure-Alls"

Dr George R Herrmann F A C P, Galveston, Tex—"Some Medical Emergencies and Their Management",

Dr Russell L Haden F A C P, Cleveland, Ohio—"The Differentiation of Ob-scure Anemia",

Dr Irvine H Page (Associate), Indianapolis, Ind—"Hypertension and Its Ex-perimental Treatment",

Dr Raymond O Muether (Associate), St Louis, Mo—"Blood Banks "

George F Lull, F A C P, Colonel (MC), U S Army, addressed the annual banquet meeting on "The Medical Officer in Our Wartime Army "

Recently Dr George C Owen (Associate) Oshkosh, Wis, was elected President and Dr Einar R Daniels (Associate), Milwaukee, Wis, Vice-President of the Wisconsin Trudeau Society

Dr Jeremiah Fletcher Lutz, F A C P, and Dr Francis R Wise, F A C P, both of York, Pa, have been appointed Chairman and Co-Chairman, respectively, of the Emergency Medical Service of York and York County

Under the Presidency of Dr Harry V Paryzek, Cleveland, Ohio, the Ohio State Medical Association held its 96th Annual Session in Columbus, April 28-30, 1942 Among the guest speakers were

Dr Chester S Keefer, F A C P, Boston, Mass—"Chemotherapy",

Dr Richard H Freyberg (Associate) Ann Arbor, Mich—"Recent Trends in the Treatment of Rheumatoid Arthritis",

Leonard G Rowntree, F A C P, Colonel (MRC), U S Army—"Health and National Defense",

Dr Frank H Krusen, F A C P, Rochester, Minn—"Physical Therapy in Gen-eral Practice"

Dr Harold I Gosline, F A C P, has been appointed Medical Director of the Ring Sanatorium and Hospital of Arlington Heights, Mass

Dr Reginald C Edson (Associate) recently resigned as Assistant Superintendent and Medical Director of the Hopemont State Tuberculosis Sanitarium and as In-structor in Medicine at the West Virginia University School of Medicine to accept the position of Assistant Director of Tuberculosis Control for the State of Con-necticut Dr Edson is now located at 36 Westfield Road, West Hartford

On January 1, 1942, Dr John Levan (Associate), Reading, Pa , was made Chief of the Department of Cardiology of St Joseph's Hospital

Dr Joseph H Barach, F A C P , Pittsburgh, Pa , addressed the Dade County Medical Society at the Jackson Memorial Hospital on April 1, 1942, in Miami, Florida. His subject was "Diabetes Mellitus The Most Scientifically Treated of All Diseases"

Dr Louis Fauquieres Bishop, Jr , F A C P , after enlisting in the Army, has been commissioned in the Medical Corps as a Major in the Army Air Forces. He has been assigned to Kelly Field, San Antonio, Texas

OBITUARIES

DR HARRY CATTELL FISLER

Dr Harry Cattell Fiser died in Jefferson Hospital on February 20, 1942 Dr Fiser, who resided in Easton, Pa , had been an Associate of the American College of Physicians since 1924

Dr Fiser received his A B and A M degrees from Lafayette College, and his M D degree from the University of Pennsylvania School of Medicine in 1895

In former years, Dr Fiser served as Laryngologist at Easton Hospital, but since 1924 he devoted most of his time to pediatrics

He was active in medical groups, having membership in the Lehigh Valley Medical Society, Northampton County Medical Society, Pennsylvania State Medical Society, and the American Medical Association

Since he had a pleasing personality, Dr Fiser was admired and liked by his professional colleagues and friends, and it is with a sense of loss that we write of his passing

EDWARD L BORTZ, M D , F A C P ,
Governor for Eastern Pennsylvania

DR ALBERT E AUSTIN

Dr Albert Elmer Austin, Old Greenwich, Conn , Fellow of the American College of Physicians since 1925, died January 26, 1942, of carcinoma of the lung

Dr Austin was born in Medway, Mass , in 1877 He attended the public schools and later entered Amherst College, where he was a member of Phi Beta Kappa, obtaining both his A B and A M degrees in 1899

After a short period of teaching, he entered Jefferson Medical College of Philadelphia, graduating in 1905 Dr Austin began the practice of medicine in Medway, but soon came to Old Greenwich where he resided until his death

In Greenwich Dr Austin had a notable career For many years he was the Director of Medical Service at both the Greenwich and the Municipal Hospitals, the latter established largely through his efforts

Dr Austin was Health Officer for twenty years, a member and Past President of the Greenwich Medical Society, member of his County, State and National Medical Societies, member of the Royal Society of Medicine in England, bank president, Representative in the State Legislature for two terms, U S Congressman from 1938 to 1940, and during the World War, Regimental Surgeon of the 214th Engineers, 14th Division, U S Army

Dr Austin was also a Thirty-third Degree Mason, well known and in great demand as an after-dinner speaker and orator on many occasions At the time of his death he was Consulting Internist to the Greenwich Hospital

His life, which was full and varied, was devoted to the service of others. His death has removed an able internist from the medical profession, and his many friends and acquaintances will feel the loss of this public-spirited citizen.

CHARLES H. TURKINGTON, M.D., F.A.C.P.,
Governor for Connecticut

DR. PHILIP FINKLE

Dr. Philip Finkle, of 1000 Park Avenue, New York City, died on March 12, 1942, from coronary thrombosis, at Miami Beach, Florida, where he moved last December expecting to practice medicine.

Dr. Finkle was born in Hartford, Connecticut, November 2, 1894. He received his A.B. degree from Columbia University in 1916 and his M.D. degree from the Columbia University College of Physicians and Surgeons in 1918. Dr. Finkle served his internship at the Mount Sinai Hospital, New York, between 1918 and 1920 and from 1920 to 1922 he was Admitting Physician to this Hospital. From 1922 to 1923 he undertook postgraduate work at the University of California, from 1923 to 1925 he did postgraduate work in physiology at the University of London in London, England, and the Kiel and Kaiser Wilhelm Institute in Berlin. Following this he did additional postgraduate work at the Hospital of the Rockefeller Institute in New York. Between 1926 and 1929, he was an Assistant in the Department of Pathology of Mount Sinai Hospital, New York. He was Chief of the Arthritis Clinic and a member of the Laboratory Research staff of Mount Sinai Hospital from 1927. From 1934 until 1939 he was Associate Visiting Physician, Harlem Hospital, New York. During 1941 he became an Officer of Instruction in Postgraduate Medicine, Columbia University College of Physicians and Surgeons.

Dr. Finkle was a Fellow of the New York Academy of Medicine, a Member of the New York County Medical Society, the Medical Society of the State of New York, the Harvey Society, the American Rheumatism Association, the American Medical Association, a Member of the Board of the Dazian Foundation for Medical Research since 1937, and he had been a Fellow of the American College of Physicians since 1940.

Dr. Finkle is survived by one brother and two sisters.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

ANNALS OF INTERNAL MEDICINE

VOLUME 16

JUNE, 1942

NUMBER 6

ADDISON'S DISEASE: EVALUATION OF SYNTHETIC DESOXYCORTICOSTERONE ACETATE THERAPY IN 158 PATIENTS*

By GEORGE W THORN, F A C P, SAMUEL S DORRANCE,† and EMERSON
DAY,‡ *Baltimore, Maryland*

INTRODUCTION

THE immediate and favorable response of patients with Addison's disease to synthetic desoxycorticosterone acetate therapy is now well established^{1, 2, 3, 4, 5} The effect which treatment with desoxycorticosterone acetate will have on the life expectancy of patients with Addison's disease cannot be stated at this early date, although our experience indicates that there has been a considerable reduction in mortality rate during the first 18 months of therapy

The present report summarizes our experience with synthetic desoxycorticosterone acetate therapy during the past three years In this period 158 patients with classical signs and symptoms of Addison's disease have been treated with the synthetic hormone Sixty-four patients have been under our direct observation in The Johns Hopkins Hospital, and 94 patients have been treated by physicians elsewhere The majority of these patients (148) have received subcutaneous implantations of pellets of crystalline hormone* following a carefully conducted assay period in which the optimum daily maintenance dose of hormone was determined by means of a single daily intramuscular injection of hormone in oil (4 to 12 weeks)

* Received for publication April 4, 1942

From the Chemical Division, Department of Medicine, The Johns Hopkins University and Hospital This study was aided by a grant from the Committee on Research in Endocrinology, National Research Council

† Dazian Foundation Fellow in Medicine, Chemical Division, Department of Medicine

‡ Emanuel Libman Fellow in Medicine, Department of Medicine

* In all instances we have used standardized sterile pellets of crystalline desoxycorticosterone acetate weighing approximately 125 mg, which were provided through the courtesy of the Ciba Pharmaceutical Products, Inc., Summit, N J

In this report data relating to the age and sex of the patients, etiology of the disease, hormone requirement and mortality rate will be presented for the entire group of 158 patients. More detailed observations relating to the course of the disease during treatment, changes in body weight, blood pressure, blood chemistry, electrocardiogram and electroencephalogram will be limited to the group of 64 patients who were directly under our observation.

TABLE I
Etiology of Addison's Disease in a Group of 158 Patients
Treated with Desoxycorticosterone Acetate

	MALE		FEMALE		TOTAL	
	Total No of Cases	Non-Tuberculous	Total No of Cases	Non-Tuberculous	Number of Cases	Non-Tuberculous
Johns Hopkins Hospital	34	80%	30	77%	64	78%
Other Cases	55	37%	39	64%	94	48%
TOTAL	89	53%	69	70%	158	60%

in The Johns Hopkins Hospital. All cases of Addison's disease which have been reported previously by us^{1, 2, 5} are included in the present report.

Etiology of the Disease. For convenience the etiological factors responsible for the adrenal cortical insufficiency in this group of patients have been classified as *tuberculous* or *non-tuberculous* (table 1). There appears to be a much lower incidence of tuberculosis of the adrenals in this group (40 per cent on the basis of clinical and laboratory diagnosis, 50 per cent on the basis of the 14 autopsy records) than has been observed previously (table 2). Conybeare and Millis⁶ noted an incidence of 76 per cent of tuberculosis

TABLE II
Etiology of Addison's Disease—Postmortem Studies (Patients Treated with Desoxycorticosterone Acetate)

Patient	Age	Sex	Classification (Clinical and Lab Studies)	Postmortem Findings—Adrenals
J. B.	52	M	Tuberculous	Tuberculosis
M. B.	31	F	Non-Tuberculous	Atrophy
R. B.	45	F	Non-Tuberculous	Atrophy
A. K.	30	F	Non-Tuberculous	Atrophy
J. L.	41	M	Tuberculous	Tuberculosis
A. M.	48	M	Tuberculous	Tuberculosis
G. M.	32	F	Non-Tuberculous	Atrophy
M. M.	27	F	Non-Tuberculous	Atrophy
S. M.	50	M	Tuberculous	Tuberculosis
S. O.	30	M	Tuberculous	Tuberculosis
O. O.	62	M	Non-Tuberculous	Atrophy
D. R.	27	F	Non-Tuberculous	Atrophy
F. S.	28	M	Tuberculous	Tuberculosis
I. T.	69	F	Tuberculous	Tuberculosis

SUMMARY

Tuberculous —7
Non-Tuberculous—7

of the adrenals in a series of 29 autopsies and Rowntree and Snell⁷ report 84 per cent in a group of 31 cases (autopsy records) of Addison's disease

Age and Sex Approximately 80 per cent of the total number of cases in this series occurred in patients 20 to 50 years of age (table 3) The average

TABLE III

Age and Sex of Patients with Addison's Disease Treated with Desoxycorticosterone Acetate

Age	Males	Females	Total
0-10	0	0	0
10-20	7	3	10
20-30	20	12	32
30-40	24	22	46
40-50	26	21	47
50-60	7	9	16
60-70	5	1	6
70-80	0	1	1
TOTAL	89 (56%)	69 (44%)	158

age of the male patients was 37.2 years and the average age of the female patients was 40.0 years, the average for the entire group of 158 patients being 38.4 years. A comparison between the number of patients in this age group and the general population (chart 1) indicates that the apparent in-

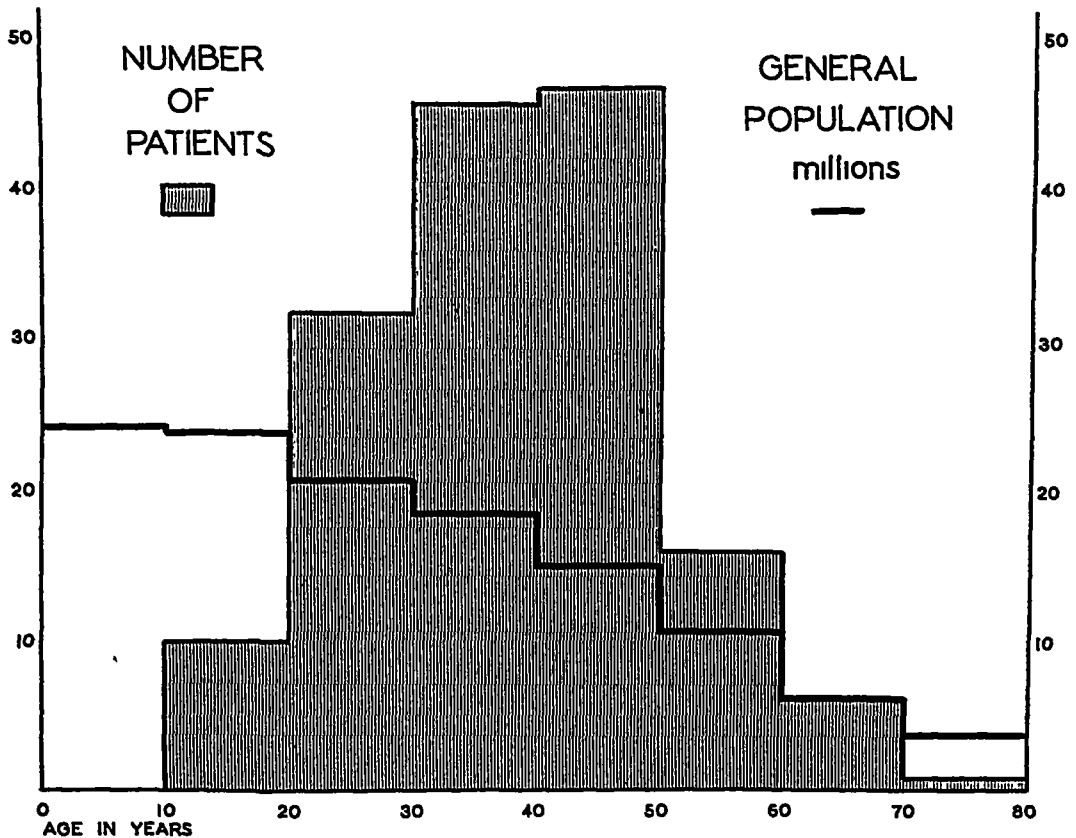


CHART 1 Age of patients with Addison's disease (158 cases)

Increased incidence of Addison's disease in this age group is real. Although the number of males predominated (table 3), the difference in incidence between the sexes was not great.

Symptomatology An analysis of the presenting symptoms in the 64 patients with Addison's disease who were seen in The Johns Hopkins Hospital is recorded in table 4. Weakness, fatigability, increasing pigmentation, anorexia and nausea were present in most instances. Ten patients (16 per cent) noted a definitely increased desire for salt and salty foods. A similar increase in "salt appetite" has been noted in adrenalectomized rats.⁸

TABLE IV
Analysis of Symptoms in 64 Patients with Addison's Disease

	Number	Per Cent
Weakness and fatigability	64	100
Increasing pigmentation	60	94
Anorexia	58	91
Nausea	55	86
Vomiting	48	75
Constipation	21	33
Abdominal pain	20	31
Diarrhea	10	16
Salt craving	10	16
Muscle pain	8	13

Diagnosis From the group of 64 patients reported from The Johns Hopkins Hospital we have excluded all in whom there was the slightest doubt regarding the diagnosis of Addison's disease. Fifty-eight of the 64 patients had been seen at some time in typical adrenal crisis. The diagnosis in the other four patients was substantiated by careful clinical observations over a period of years. In the 94 patients who were not under our direct care we have relied upon the diagnosis of Addison's disease as established by the attending physician. In most instances these patients have also been seen in adrenal crisis and have, in addition, exhibited the changes characteristic of the syndrome, i.e., increasing pigmentation, hypotension, weakness, weight loss, anorexia and hypochloremia. The diagnosis of Addison's disease was substantiated in each instance in which a postmortem examination was made.

Desoxycorticosterone Acetate Therapy: In most patients treatment with desoxycorticosterone acetate was initiated by administering a daily intramuscular injection of the synthetic hormone in sesame oil (Percorten, Ciba, Inc.) containing 5 mg of hormone) with or without supplementary sodium chloride therapy. The majority of patients required 5 mg or less of Percorten daily (table 5) with 4 gm (average) of supplementary sodium chloride medication. Less than 10 per cent of the patients required more than 5 mg of hormone daily. The initial dose of hormone was usually much greater than the ultimate maintenance dose, since most patients were in rather

poor condition at the time synthetic hormone therapy was instituted. As their condition subsequently improved under desoxycorticosterone acetate treatment, the hormone requirement decreased considerably. However, it often required several weeks before the minimum maintenance dose was attained.

Although supplementary sodium chloride therapy was not required in order to obtain successful regulation with the synthetic hormone,² it was used in most instances because it greatly reduced the hormone requirement and hence the cost of therapy. For most patients this was a consideration

TABLE V

Daily Maintenance Dose of Desoxycorticosterone Acetate in Sesame Oil of 141* Patients with Addison's Disease

Daily Dose of Hormone mg.	Number of Patients
0-1	0
1-2	53
2-3	20
3-4	8
4-5	48
5-10	8
10+	4
3.8 mg. per day, average	141 patients

* Assays in 17 patients were not standardized sufficiently to warrant inclusion in this table.

which could not be neglected. However, at present, 60 patients are being maintained with pellets of synthetic hormone *without* supplementary sodium chloride therapy. Supplementary sodium chloride therapy was best tolerated when given in the form of 1 gm. *enteric coated tablets*, at meal time *with food*, a total of 3-5 gm. per day being the quantity most frequently used. It is undesirable to administer more than 5 gm. of supplementary sodium chloride therapy daily to most patients, even though well tolerated, since the onset of an acute infection or gastrointestinal disorder is usually accompanied by an inability to take the sodium chloride tablets and hence the patient is suddenly deprived of a large part of his therapy at a time when his need is greatest. A supplement of 3 gm. of sodium chloride daily was always used when patients were being prepared for pellet implantation (*vide infra*). Sodium chloride therapy in conjunction with desoxycorticosterone acetate treatment is *contraindicated* in patients who are predisposed to edema formation, hypertension or circulatory insufficiency.

The desirability of implanting pellets of crystalline hormone was considered after a patient had been maintained in good condition for a period of one month or more with daily injections of Percorten (crystalline hormone in sesame oil). Pellets were implanted in 148 of the patients in this group (table 6) after careful clinical control had permitted the daily requirement of hormone in oil to be determined accurately (table 5). In most instances it re-

quired at least four weeks to determine the optimum maintenance dose of hormone.

Calculation of Pellet Requirement: The number of pellets (Ciba; 125 mg. each) to be implanted was calculated directly from the daily maintenance dose of hormone in oil, injected intramuscularly. One pellet of 125 mg.* was implanted for each 0.5 mg. of hormone so required by daily injection.

TABLE VI
Initial Pellet Requirement of Patients with Addison's Disease

Number of Patients	Average Number of Pellets of Crystalline Desoxycorticosterone Acetate †	Total Quantity of Hormone per Patient (Aver.)
148*	6.4 (Range 2-15)	820 mg. (Range 250-1875)

* 10 patients have been treated with intramuscular injections of hormone in oil (Percorten) only.

† Pellets weighed 125 mg. \pm 6 mg.

A small constant quantity of supplementary sodium chloride medication (3 gm. daily) was administered during the period of assay. This provided a balancing mechanism which could be used after pellets were implanted to compensate for any temporary excess of hormone. Thus, in the event that excessive sodium chloride was retained (edema) following pellet implantation it was possible to correct this by discontinuing a part or all of the added sodium chloride medication. If necessary, sodium chloride in the diet could also be restricted. Maintaining the sodium chloride therapy at a low dosage level (3 gm. daily) permitted an appreciable increase in the quantity of supplementary sodium chloride at a later date, should this be desirable. In this way a temporary need for additional therapy might easily be met by increasing the quantity of sodium chloride therapy. This could not have been done had the patient been receiving large doses of sodium chloride.

Pellets, weighing 125 mg. each, provided effective therapy in most patients for a period of at least 12 months. The fact that pellets were no longer providing an adequate supply of hormone was first indicated in most instances by a gradual reduction in blood pressure. Later fatigue, loss of weight and appetite were observed. However, in most instances, as soon as the reduction in blood pressure was noted, without awaiting the further development of symptoms of adrenal insufficiency, the patient was given intramuscular injections of hormone. One injection of 2 to 5 mg. (0.4 to 1.0 c.c.) of Percorten, twice weekly, was adequate for most patients at this

* Standardized pellets of desoxycorticosterone acetate prepared by Ciba Pharmaceutical Products, Inc., Summit, N. J., were used throughout these studies. The rate of absorption of these pellets has been shown to be 0.3 to 0.5 mg. per day per pellet. Pellets prepared in a different manner with a different rate of absorption should not be implanted on the basis of the calculation used in these studies, i.e., 1 pellet of 125 mg. for each 0.5 mg. of hormone required by daily injection.

time. Later daily injections of the hormone were resumed and a new assay was conducted. Three grams of sodium chloride daily were administered during this new assay period. When the maintenance hormone requirement had again been ascertained, and when it was certain that little, if any, of the original pellets remained, new pellets were implanted. *New pellets of desoxycorticosterone were never implanted arbitrarily at the end of one year, on the basis of the original assay* for two reasons: first, patients' hormone requirement often changed considerably after a year of sustained therapy; secondly, in many patients at the end of 12 months, there was still an appreciable quantity of hormone which was being absorbed from the original pellets and which would have led to overdosage if supplemented by a full complement of new pellets. At present 61 of the patients have received two or more implantations (table 7). The average duration of time which

TABLE VII
Number of Implantations of Pellets of Crystalline Desoxycorticosterone Acetate

Number of Implantations	Number of Patients
1	148
2	61
3	12
4	1
Total Number of Implantations	222

elapsed between the first and second implantations was 12.3 months. In most patients supplementary injections of hormone in oil were not required during the first 12 months subsequent to the initial pellet implantation.

Technic of Pellet Implantation: The infrascapular region posteriorly was selected for pellet implantation. Strict asepsis was observed. The operative field was prepared with iodine and alcohol and the site of incision was infiltrated with procaine, 1:200 solution. A transverse incision 2 to 4 cm. in length was made a few centimeters below the inferior spine of the scapula. With blunt dissection a number of small pockets, 2 to 3 cm. in depth were prepared in the subcutaneous tissues. The opening of each pocket was held far enough apart by a nasal dilator to permit pellets to be dropped gently to the bottom of the pocket without the use of force. This was important, for if the opening into the pocket were too small the fragile pellet could easily be crushed by the force used to insert it; furthermore, if the pocket were not deep enough, the pellet might be extruded subsequently through the incision. The wounds were closed with subcuticular stitches of fine black silk. It was possible to insert as many as 10 to 15 pellets through a single incision.⁵

At present 131 of the 132 patients now alive are being treated with pellets of hormone. Of this number 60 are receiving *no supplementary sodium chloride medication* at present. Six patients in addition to desoxycorti-

costerone acetate treatment are receiving 3 to 6 c.c. daily of adrenal cortex extract (Wilson, Upjohn or Parke, Davis & Co.). Supplementary injections of synthetic hormone in oil (Percorten, Ciba), intravenous administration of saline and glucose solutions and large doses of adrenal cortex extract, 5 to 10 c.c. at 4 to 8 hour intervals have been administered to many of these patients during the course of acute infections or in preparation for operative procedures.

The sublingual administration of desoxycorticosterone acetate in propylene glycol according to the method of Anderson et al.⁹ has been tested in five patients with Addison's disease.¹⁰ It was shown that this method was effective, but not efficient (table 8). It appears that administration of hor-

TABLE VIII

Relative Effectiveness of Desoxycorticosterone Acetate Administered Subcutaneously (Pellets), Intramuscularly, and Sublingually

	Equivalents
Subcutaneous implantation of pellets of crystalline hormone	1.2 mg. daily
Intramuscular injection of hormone in oil (once daily)	2.0 mg. daily
Sublingual administration of	
(a) Desoxycorticosterone acetate in propylene glycol	6.0-8.0 mg. daily
(b) Solid tablets of crystalline hormone in glucose	6.0-8.0 mg. daily

mone sublingually may be useful in the treatment of patients whose hormone requirement is small and who are able to afford the increased quantity of hormone required by this route of administration. Recently we have tested solid tablets of crystalline desoxycorticosterone acetate "Linguets"* for sublingual administration and have found them very much more convenient to administer than the hormone in propylene glycol although the tablets are no more efficient than hormone in propylene glycol administered sublingually. The results obtained on a comparative assay of "Linguets" and Percorten are presented in chart 2. Patients receiving desoxycorticosterone acetate sublingually are not immune from the complications which have been reported in patients treated with intramuscular injections or subcutaneous implants of hormone. In patient M. D. edema readily developed when the dose of hormone, administered in propylene glycol sublingually, was increased above the minimum maintenance dose.

Results of Therapy: The mortality rate for the entire group of 158 patients was 15.4 per cent for a period of 1.7 years of therapy, or an annual mortality rate of 9.2 per cent, per year (table 9). A comparison with earlier reports on the life expectancy of patients with Addison's disease before the

* Tablets ("Linguets") composed of desoxycorticosterone acetate (1, 2, 5 and 10 mg. respectively), lactose, sucrose, talcum and gum arabic for sublingual use were prepared by Ciba Pharmaceutical Products, Inc.

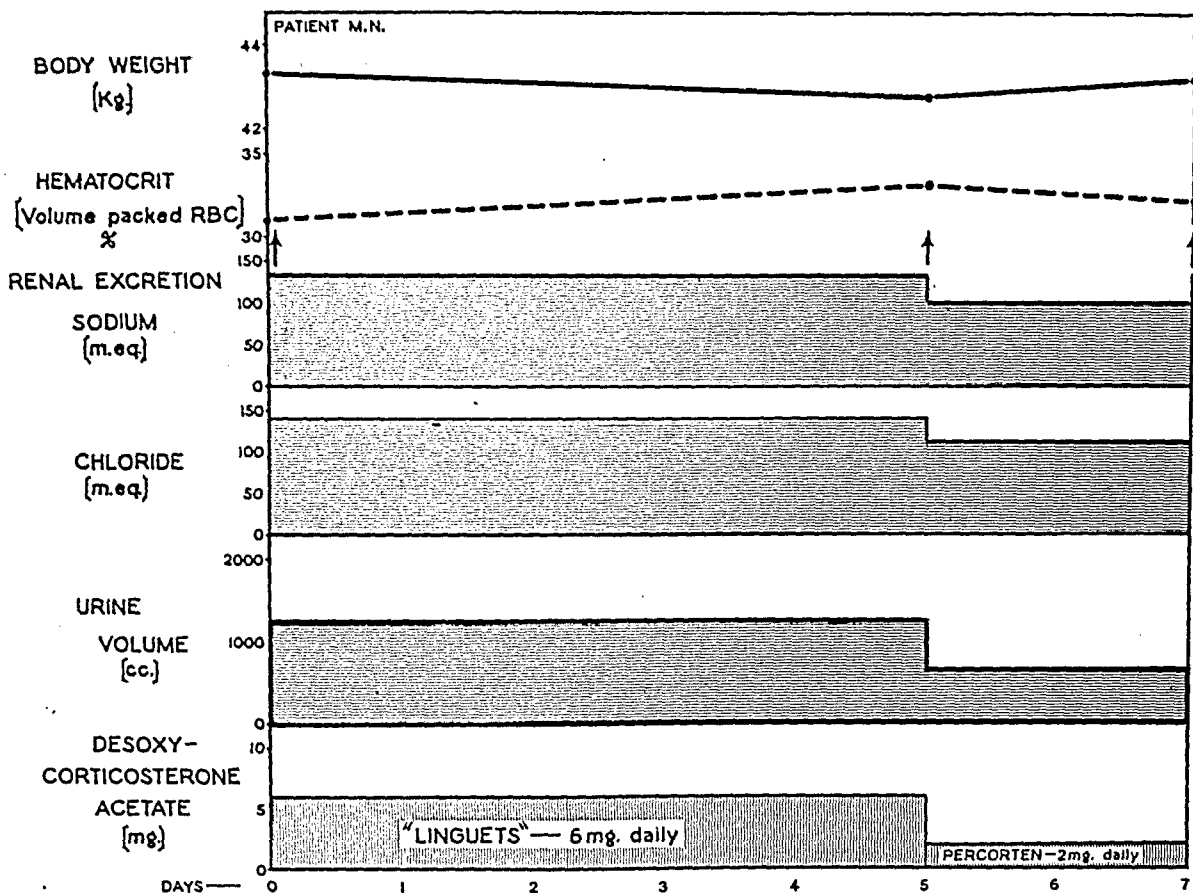


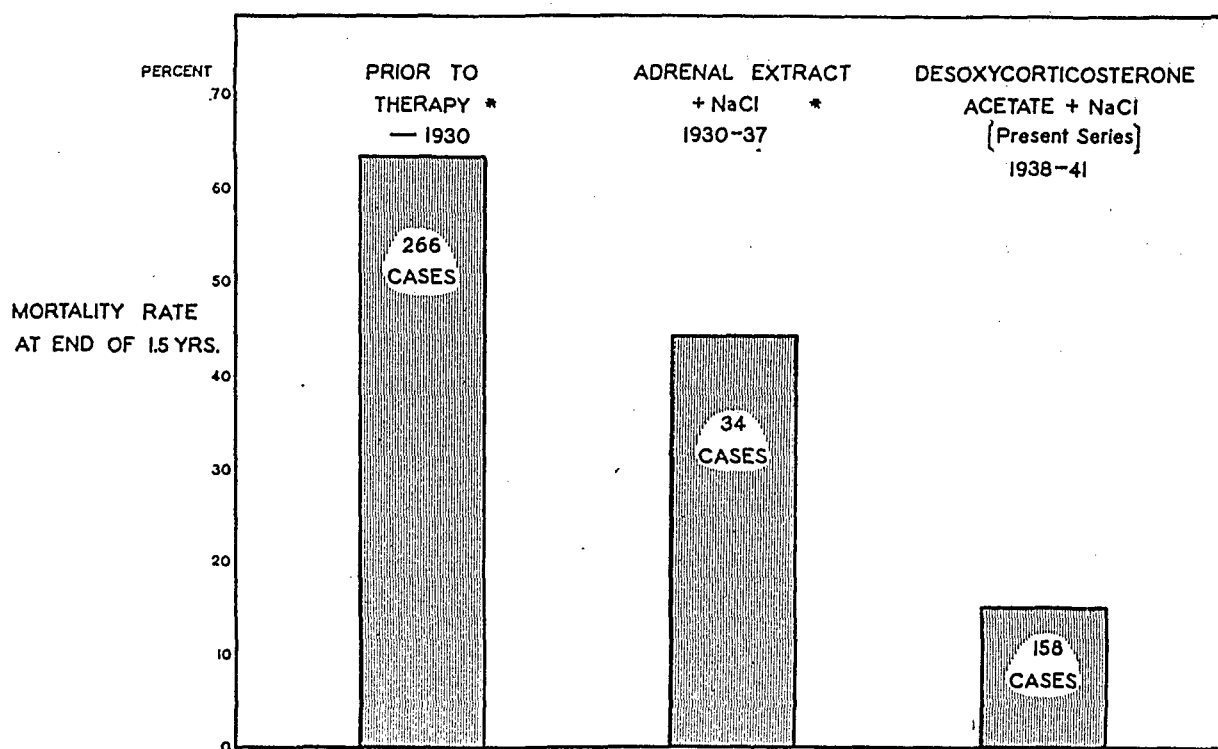
CHART 2. The relative effectiveness of desoxycorticosterone acetate tablets ("linguets") for sublingual use, and a single daily injection of synthetic hormone in oil ("percorten").

TABLE IX
Mortality Rate in 158 Patients with Addison's Disease Treated with Desoxycorticosterone Acetate

	Number of Patients	Duration of Therapy	Number of Deaths	Mortality Rate
Johns Hopkins Hospital...	64	1.8 yr.	10	16.0%
Other Cases.....	94	1.6 yr.	14	14.9%
TOTAL.....	158	1.7 yr.	24	15.2%

era of specific therapy and during the period of extract and sodium chloride therapy has been made (chart 3). The possible rôle played by added sodium chloride therapy in the present series of cases is controlled by the mortality rate which was observed when combined extract and sodium chloride therapy were employed (44.2 per cent at the end of 1.5 years). In regard to the group treated with adrenal cortex extract it is only fair to state that in all likelihood these patients did not, for the most part, receive adequate hormone therapy. There is no doubt, however, that they received all of the sodium chloride medication which they could tolerate. Thus, the mortality rate for

this group more correctly represents the mortality rate for a group of patients who received adequate sodium chloride therapy, but, for the most part, inadequate extract therapy. The reasons for the latter were, and still remain, the high cost of adrenal cortex extract therapy and the necessity for frequent injections of this hormone preparation if the best clinical results are to be obtained.



* C. H. GREENE—ARCH. INT. MED. 1937

CHART 3. Comparative mortality rates in patients with Addison's disease prior to and subsequent to use of specific therapy.

Not only was the mortality rate greatly reduced in the group of patients treated with desoxycorticosterone acetate but the clinical improvement in the majority of patients was very striking. At this point it may be of interest to quote from Rowntree⁷ who stated prior to the use of specific hormone therapy: "Most patients with Addison's disease are invalids throughout the course of the disease. Not more than one patient out of four or five is rehabilitated even to 50 per cent of former working capacity for as long as one year, and not more than one in sixty is rehabilitated to the extent of 75 to 80 per cent of previous working capacity for five years. None of the patients in our series has been completely restored to health and normal strength." In the group of 64 patients studied in the Johns Hopkins Hospital there occurred an average gain of approximately 4 kg. during the 1.7 years of therapy (chart 4). There was also a corresponding rise in blood pressure from an average level of 100 mm. Hg systolic and 66 mm. diastolic prior to therapy to a level of 126 mm. Hg systolic and 76 mm. diastolic at present.

Statistical analysis of these data indicates that the changes in all instances are significant.* The factor for difference between means is 4.9 in respect to the values for body weight, 6.3 for systolic blood pressure values, and 6.5 for diastolic pressure values.

A total of 31 of the 64 patients in our group improved so markedly during desoxycorticosterone acetate treatment that they were fully rehabilitated

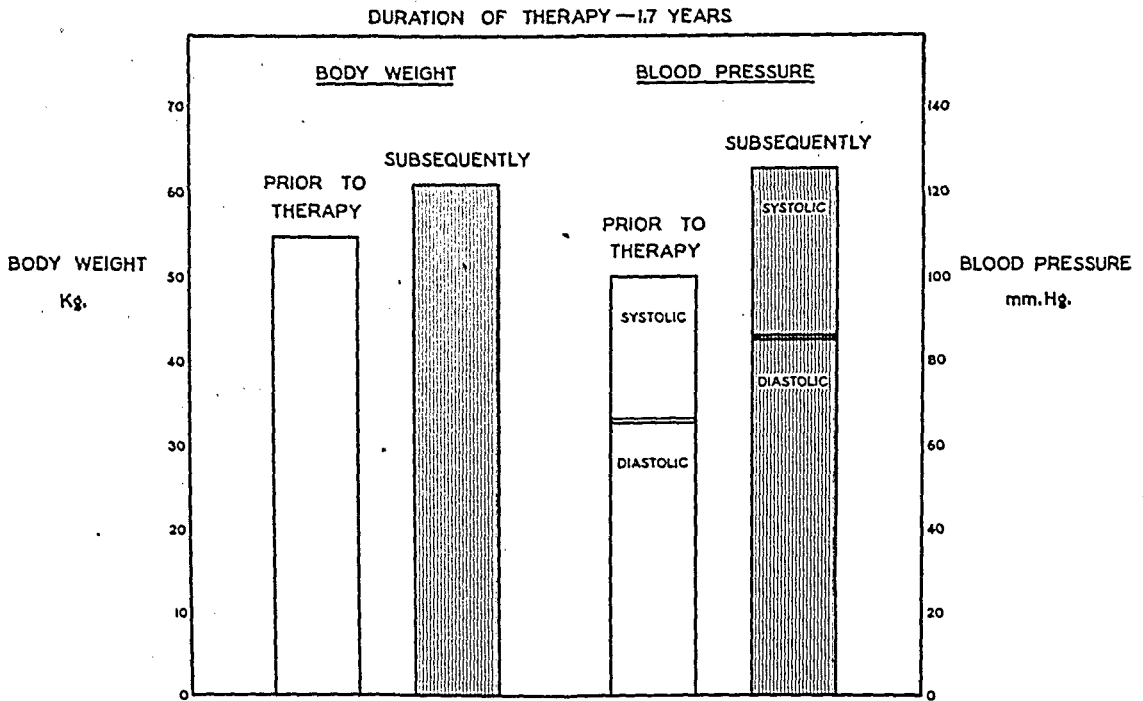


CHART 4. Effect of desoxycorticosterone acetate therapy in Addison's disease (Johns Hopkins Hospital—64 patients).

(table 10). Nineteen of these 31 patients were males. All 19 of these male patients are employed *full time* at present (table 11). Sixteen patients (25 per cent) have been greatly improved by therapy but cannot be considered to have been restored completely to normal strength and activity; in five of these 16 patients there is a complicating disease which will prevent these patients from returning completely to normal health (table 10, footnote 2). Seven patients in the group of 64 have shown little or no improvement. In four of these patients there is a definite complication (table 10, footnote 3); in the remaining three there is no apparent reason for the failure of desoxycorticosterone acetate therapy. The therapeutic results which were achieved in the outside group of patients (94) approximated closely the results which were obtained in the Johns Hopkins Hospital group.

*The difference between means is significant when the value of this factor is greater than 2.

See footnote to table 22.

TABLE X

Summary of Present Status of 64* Patients with Addison's Disease (Johns Hopkins Hospital) Treated with Desoxycorticosterone Acetate

	Number	Per Cent
<i>Striking improvement</i> (fully rehabilitated)	31	48
<i>Improved</i> —but not fully rehabilitated†	17	27
No improvement‡	6	9
Deaths	10	16

* 62 of these patients have been treated with subcutaneously implanted pellets.

† This group includes 3 patients with tuberculosis and 2 patients with rheumatic heart disease.

‡ This group includes 1 patient with tuberculosis; 1 patient with coronary infarction; 1 patient with marked hypertension which antedated onset of Addison's disease.

The immediate causes of death in the 10 patients in the Hopkins group and in the 14 patients in the outside group have been listed in table 12. Acute intercurrent infections and cardiovascular accidents account for more than 50 per cent of the deaths. These complications will be considered in some detail later. The two patients who died from hypoglycemia represent, in our estimate, preventable deaths, if preparations with "carbohydrate-reg-

TABLE XI

Effect of Desoxycorticosterone Acetate Therapy on Rehabilitation of Male Patients with Addison's Disease (Johns Hopkins Hospital)

Total Number of Male Patients	Number now Employed Full time	Per Cent
34	19	56%

ulating" potency had been used. In neither instance was the patient able to afford supplementary extract therapy.

In addition to the disturbance in carbohydrate metabolism which persisted in patients adequately treated with desoxycorticosterone acetate certain other signs and symptoms of adrenal insufficiency also failed to respond to continued hormone therapy in a small proportion of the patients. Thus, four patients (approximately 6 per cent of the Johns Hopkins Hospital

TABLE XII

Immediate Causes of Death in 24 Patients with Addison's Disease (Entire Group of 158 Patients)

	Number	Per Cent
Acute intercurrent infections	7	29
Cardiovascular disease	7	29
Tuberculosis	4	17
Hypoglycemia	2	8
Discontinued therapy	1	4
Unexplained	3	13
TOTAL	24	

group) lost weight during a prolonged period of desoxycorticosterone acetate treatment (2.5 years, average duration of treatment). In six of the patients (approximately 10 per cent) an appreciable degree of muscular weakness and asthenia persisted. In three patients (approximately 5 per cent) anorexia, nausea, and occasionally vomiting were observed.

Disturbances in Carbohydrate Metabolism: Recent studies¹¹ have increased our understanding of the nature of the disorder in carbohydrate metabolism which occurs in patients with Addison's disease. It now appears that any or all of the following defects may be observed in these patients:

1. Decreased rate of absorption of glucose from the gastrointestinal tract (flat glucose curve).
2. Increased utilization of carbohydrate.
3. Impaired ability to form new carbohydrate from non-glucose sources, i.e., "impaired gluconeogenesis."
4. "2" and "3" facilitate depletion of liver glycogen reserves and consequently predispose to hypoglycemia.
5. Lowered threshold at which signs and symptoms of hypoglycemia become evident.

Patients with Addison's disease vary widely in the extent to which disturbances in carbohydrate metabolism complicate their illness. Some patients develop hypoglycemia only during the course of intercurrent infections, prolonged fasting, or other stresses, whereas other patients have been known to display signs and symptoms of hypoglycemia after a brief postponement of a meal. To detect underlying disturbances in carbohydrate metabolism we have tested 52 of our patients with an intravenous glucose tolerance test* in which the development of moderate or severe signs and symptoms of *hypoglycemia* two to three hours after the intravenous administration of glucose signifies the presence of a rather profound disturbance in carbohydrate metabolism.¹¹ Of the group of 52 patients tested, 39 developed marked signs and symptoms of hypoglycemia two to three hours after the glucose solution had been injected intravenously (table 13). Twenty-six of these 39 patients had experienced similar episodes of hypoglycemia spontaneously. In 13 of the patients the positive reaction to this test constituted the first clinical evidence of a disturbance in carbohydrate metabolism. Thirteen patients in the group of 52 gave no evidence of the existence of any disturbance in carbohydrate metabolism by this test, and no history of spontaneous hypoglycemic episodes.

* *Standard Intravenous Glucose Tolerance Test.* Glucose, 0.5 gm. per kg. body weight, is injected intravenously as a 20 per cent solution in *distilled water*. The rate of flow is so adjusted that the infusion is completed in 30 minutes. Capillary blood for sugar determinations is taken in the fasting state and at 30 minute intervals for three to four hours following the completion of the infusion. Urine specimens are collected at appropriate intervals and analyzed for sugar.

It is of interest to note that restoration of plasma volume, plasma electrolyte concentration and blood pressure to normal levels by means of desoxycorticosterone acetate therapy does not correct the underlying disturbance in carbohydrate metabolism.¹¹ Only the gastrointestinal absorption of glucose is facilitated by synthetic hormone therapy, whereas treatment with adrenal cortex extract (large doses [50 c.c.] by injection) or certain, naturally occurring, crystalline adrenal steroid compounds (corticosterone, dehydrocorticosterone, 17-hydroxy-dehydrocorticosterone) promotes gluconeogenesis, depresses glucose utilization, increases liver glycogen stores

TABLE XIII

Incidence of Abnormal Carbohydrate Metabolism in 52 Patients with Addison's Disease
(Johns Hopkins Hospital)

	Number of Patients	Per Cent
Spontaneous hypoglycemia	26	50
Hypoglycemia induced by intravenous glucose tolerance test	39	75
No evidence of disturbance in carbohydrate metabolism	13	25

and raises blood sugar levels.^{11, 12} Unfortunately adrenal steroids with "carbohydrate-regulating" potency are not as yet available for clinical use, and adrenal cortical extract in quantity sufficient to affect carbohydrate metabolism significantly cannot be afforded by most patients. Thus, with the exception of the use of adrenal cortex extract therapy in patients in crisis, the treatment of hypoglycemia consists primarily in attempting to prevent its occurrence by the use of frequent feedings of a diet high in readily available carbohydrate content.

Treatment of Adrenal Crisis: In most instances intercurrent infections were responsible for the precipitation of adrenal crises in patients treated with desoxycorticosterone acetate. In a few patients the development of hypoglycemia, spontaneously, acted as the exciting factor. Of all infections, those due to streptococcus appeared to be the most frequent and most severe. Because of the rapidity with which crisis is precipitated during the onset of acute respiratory infections, treatment must be instituted immediately, if possible. The use of sulfadiazine is of great aid in the treatment of streptococcus infections in patients with Addison's disease.¹³

The aims of therapy in patients in crisis or in impending crisis may be summarized as follows:

1. Support of plasma volume and blood pressure by
 - (a) Intravenous infusion of sodium chloride (0.9 per cent solution) and dextrose (5 to 10 per cent solution).
 - (b) Aqueous adrenal cortex extract (intravenously and subcutaneously) in large quantities.

- (c) Synthetic desoxycorticosterone acetate in oil (intramuscularly) to supplement maintenance dose.
- (d) Epinephrine in oil (0.5 c.c.) intramuscularly if systolic blood pressure falls below 90 mm. Hg.

2. Prevention of hypoglycemia.

- (a) Infusions of dextrose (see 1 a).
- (b) Frequent feedings of readily available carbohydrate as soon as tolerated
- (c) Large quantities of adrenal cortex extract (1 b).

3. Antibacterial chemotherapy whenever indicated.

4. Plasma and whole blood transfusions are not recommended as routine procedures.

Suggested Outline of Therapy: 1. The patient is placed in a warm bed with adequate blankets and is *immediately given an intravenous infusion of 1,000 to 1,500 c.c. of sodium chloride 0.9 per cent and glucose 5 to 10 per cent.* This is repeated in 12 hours and is given subsequently at least once daily until the temperature has reached normal or until the patient is taking fluids and eating well.

2. Twenty-five c.c. of aqueous adrenal cortex extract are added to the infusion and in addition 10 c.c. of extract are injected subcutaneously. The subcutaneous injection of 5–10 c.c. of aqueous extract (Wilson, Upjohn or Parke, Davis) is repeated every two to four hours until fever subsides, then every four to eight hours until the patient is eating well.

3. Twenty milligrams of desoxycorticosterone acetate in oil are injected intramuscularly in divided doses immediately; and thereafter 5 to 10 mg. are given once daily depending upon blood pressure, quantity of saline solution which has been administered, appearance of excessive fluid retention, etc.

4. One c.c. of epinephrine in oil injected intramuscularly is indicated if the level of systolic blood pressure falls below 90 mm. Hg.

5. Blood pressure determinations are made at intervals of one to two hours, day and night. Small quantities of fruit juice with added lactose, or ginger ale, are given at frequent intervals if tolerated. Since 1,500 c.c. of saline and dextrose solution are given intravenously at 8 to 12 hour intervals, additional fluid or sodium chloride by mouth is not essential during the first 24 hours of treatment. A fall in blood pressure without signs of excessive sodium chloride and water retention is a definite indication for increasing the infusions of sodium chloride and for giving additional desoxycorticosterone acetate intramuscularly (5 to 10 mg.). A fall in blood pressure in the presence of excessive sodium chloride and water retention is a definite indication for reducing the number of infusions, for discontinuing the desoxycorticosterone acetate therapy and for *increasing* the quantity of adrenal cortex extract, i.e., 10 c.c. every hour. *At this time a plasma transfusion*

should be seriously considered. Our experience with the unfavorable reaction of patients with Addison's disease to whole blood transfusions suggests that this therapeutic procedure should be withheld unless other measures fail.

As a precautionary measure we urge that all patients with Addison's disease keep on hand *at all times or have immediate access to the following:*

Emergency Kit:

1. 1000 c.c. of 0.9 per cent NaCl and 5 to 10 per cent glucose solution for intravenous administration.
2. Sulfadiazine tablets.
3. Adrenal cortex extract, 50 c.c. (Wilson, Upjohn, Parke-Davis).
4. Synthetic desoxycorticosterone acetate in oil, 10 c.c. (Percorten, Ciba; Cortate, Schering; Doca, Hoffmann-LaRoche).

Complications Which May Arise During Desoxycorticosterone Acetate Therapy.

1. *Non-specific:* Hypoglycemia occurs not infrequently in patients treated with desoxycorticosterone acetate alone. This complication has already been referred to (see "Disturbances in carbohydrate metabolism"). Treatment consists in frequent feedings of a diet high in readily available carbohydrate and supplementary injections of aqueous adrenal cortex extract, 5 to 10 c.c. every four to six hours.

In two patients intramuscular injections of desoxycorticosterone acetate in sesame oil (Percorten) were accompanied by localized redness, pain and tenderness at the site of the injection, as well as fever and malaise. It was demonstrated subsequently that these reactions were due to the injection of sesame oil and not to synthetic hormone.⁵ Both patients did well when pellets of crystalline hormone were implanted.

On four occasions in over 200 pellet implantations pellets were extruded from the site of the incision. Such complications may be avoided by placing the pellets a distance of at least 2.5 cm. from the margin of the incision. In no instance thus far has a local infection occurred at the site of the implantations.

2. *Specific:* Most of the complications which occur in patients with Addison's disease treated with desoxycorticosterone acetate (intramuscular injections of hormone in oil, pellets of crystalline hormone implanted subcutaneously or hormone administered sublingually) may be accounted for by one factor, i.e., *excessive retention of sodium chloride and water*. The extent to which untoward signs and symptoms develop is dependent upon

- (a) the dose of hormone;
- (b) the amount of sodium chloride in the diet and the supplementary sodium chloride therapy;
- (c) predisposing factors in certain patients, such as heart disease, hypertension, hypoproteinemia, etc.

The nature of the complications which have arisen in 64 patients (Johns Hopkins Hospital) treated with synthetic hormone is summarized in table 14. *Hypertension* was noted at some time during therapy in 22 or 35 per cent of the patients. In most instances the hypertension was of a transient nature and occurred only during a period of excessive hormone and supplementary

TABLE XIV

Incidence of Complications Associated with Desoxycorticosterone Acetate Therapy (Johns Hopkins Hospital—64 Patients)

	Number of Patients	Per Cent
Hypertension*	22	34
Edema	17	27
Cardiac decompensation	5	8
Tendon "contractures"	2	3
Transient paralysis	1	2

* Systolic blood pressure exceeding 150 mm. Hg or diastolic blood pressure exceeding 100 mm. Hg or both, at some time during course of therapy.

sodium chloride therapy. In patients with Addison's disease in whom some degree of hypertension existed prior to the onset of adrenal cortical insufficiency there was a great predilection for the blood pressure to return to high levels and to remain there with only moderate doses of hormone.

Transient edema was noted in 14 (23 per cent) of the patients during desoxycorticosterone acetate therapy. In three of these patients the edema was rather extensive (anasarca). Edema was most frequently observed during the early weeks of therapy when an attempt was being made to determine the patient's optimum maintenance dose of hormone. The edema subsided rapidly following a reduction in the dose of hormone or upon withdrawing supplementary sodium chloride medication. In patients with long standing thrombophlebitis or lymphatic obstruction it was difficult to administer the optimum maintenance dose of hormone without at the same time inducing a moderate degree of localized edema in the affected part.

In five patients (8 per cent) continued synthetic hormone therapy accompanied by a marked increase in plasma volume, body weight, blood pressure and physical activity, ultimately induced signs and symptoms of circulatory failure. This complication occurred only in elderly patients or in patients in whom there had been some evidence of preëxisting myocardial damage or vascular disease. Circulatory failure may usually be avoided if care is exercised in restricting sodium chloride intake and in restricting activity during the early period of therapy during which blood volume, blood pressure and body weight are increasing rapidly. Treatment for this complication consists in absolute bed rest, digitalization, reduction in hormone and elimination of sodium chloride from diet. Subsequent rehabilitation should proceed slowly.

The long continued administration of even moderately excessive quantities of desoxycorticosterone acetate, or the synthetic hormone in conjunction with supplementary sodium chloride therapy may result in the excessive retention of sodium and chloride in the blood serum and tissues¹⁴ associated with an abnormally low concentration of potassium. The resulting disturbance in sodium-potassium ratio, which is just the antithesis of the ratio which obtains in adrenal insufficiency (table 15) may give rise to unusual complications characterized by disturbances in neuromuscular function. In one patient (J. Z.) transient peripheral extensor motor paralysis was observed in conjunction with a low serum potassium concentration.⁵ The

TABLE XV
Changes in Sodium to Potassium Ratio Which May Occur During
Excessive Desoxycorticosterone Acetate Therapy

	Serum Sodium m.eq./l.	Serum Potassium m.eq./l.	<u>Sodium</u> <u>Potassium</u>
Adrenal crisis.....	120	8.0	15
Adequate treatment.....	140	4.6	30
Excessive treatment.....	145	3.2	45

rapidity of onset, the absence of sensory disturbances and the rapid recovery without sequelae suggested an episode similar to that which is observed in familial periodic paralysis. Experimentally, similar disturbances have been noted in dogs treated with excessive doses of synthetic hormone in conjunction with supplementary sodium chloride.¹⁵ As might be anticipated, a diet low in potassium content (of the type formerly recommended in the treatment of Addison's disease before the advent of desoxycorticosterone acetate) would facilitate these changes. For this reason it is urged that patients with Addison's disease treated with desoxycorticosterone acetate *not be given a diet of low potassium content!*

A second type of complication which has been observed in two of the 64 patients in our group, and in one patient in the outside group of 94 patients, consists of a painful and disabling contracture of the thigh muscles and tendons. The onset of this complication has occurred after several weeks or months of continued hormone therapy. Thus far it has been observed only in patients who have been incapacitated because of marked weakness or because of arthritic involvement of the knee joints. At the onset, because of the periarticular reference of the pain, it was thought that the patients were suffering from a relapse of the underlying arthritis. During the progress of the illness, the thighs slowly became flexed on the abdomen and the patients were unable to walk because of inability to straighten their legs. Roentgenograms of the joints revealed no evidence of progressive articular change. Although contractures conforming to this type have been seen in a patient with Addison's disease prior to therapy, it seemed probable that synthetic hormone therapy might have been a precipitating factor, since

in all three of these patients the onset of symptoms occurred after a continued period of hormone therapy. It is possible that this complication may be caused by excessive sodium and chloride retention in tissues, particularly tendons. No doubt inactivity and preëxisting joint disease predispose a patient to these changes.

Treatment of this complication, thus far, has been unsatisfactory. Obviously, sudden withdrawal of hormone would precipitate a crisis. Elimination of added sodium chloride therapy, reduction of synthetic hormone to a minimum maintenance dose, and supplementary potassium medication (potassium citrate solution 10 per cent; 30 to 45 c.c. in fruit juice daily) would be indicated if it could be proved that excessive sodium retention actually induced the change. In one patient we have resorted to orthopedic measures (traction followed by manipulation under anesthesia), since a trial on the above regimen, and a continued period of adrenal cortex extract therapy did not result in any appreciable improvement in this patient. Attention is called to this condition particularly because of the ease with which it may be confused with the muscular pains (low-sodium cramps) which are commonly observed in patients in adrenal insufficiency. For the latter, sodium chloride and hormone are specific.

Although desoxycorticosterone is closely related chemically to progesterone we have not, to date, observed any evidence of progestational changes in female patients with Addison's disease who have been treated for long periods of time with the synthetic adrenal cortical hormone. Several patients have noted increased turgor of the breasts. It seems reasonable to assume that this change may be accounted for by an increased accumulation of extracellular fluid which occurs during adrenal cortex hormone therapy.

Cardiac Changes in Addison's Disease: It has long been known that the heart in patients with Addison's disease is smaller than normal⁷ and that the electrocardiogram in many of these patients shows abnormalities suggesting disease of the myocardium.^{16, 17} Recent studies^{4, 18, 19, 20} have demonstrated that progressive cardiac enlargement may occur in patients with Addison's disease following overdosage with desoxycorticosterone acetate. It seems probable that preëxisting cardiac disease may play an important rôle in predisposing certain patients to myocardial failure following excessive desoxycorticosterone acetate therapy. The poor physical condition of untreated patients with Addison's disease makes a study of cardiac reserve difficult, if not impossible, prior to therapy. Investigation of the effect of synthetic hormone therapy on cardiac function, therefore, is dependent chiefly on a study of the progressive changes in electrocardiograms and teleroentgenograms.

The effect of synthetic hormone therapy on changes in cardiac diameter was followed closely in 46 of our 64 patients studied (table 16). In no patient did the heart-to-chest ratio exceed 50 per cent prior to therapy. In two patients during therapy the ratio exceeded 50 per cent and both of these

TABLE XVI
Effect of Desoxycorticosterone Acetate Therapy on Cardiac Diameter
(46 patients)

	Heart to Chest Ratio	Range
Prior to treatment	38.6%	(28-46)
Maximum measurement during treatment	42.2%	(32-55)
Present status (approx. 2 yrs. therapy)	41.3%	(32-50)

patients were among the five who developed signs of circulatory insufficiency. With care in the regulation of the dose of hormone and supplementary sodium chloride medication, only a moderate increase in heart size occurred during a period of approximately two years of treatment, viz., 38.6 per cent heart-to-chest ratio prior to therapy; present status 41.3 per cent heart-to-chest ratio.

Electrocardiograms were analyzed in 58 of our 64 patients to determine the incidence of abnormal changes without regard to therapy (tables 17 and 18). There were significant electrocardiographic changes in 35 of the patients (60 per cent). In 17 patients (29 per cent) the changes suggested definite myocardial damage. A high incidence of abnormal electrocardiograms appeared in all age groups (table 17). It is interesting to note that 19 of the patients (54 per cent) with abnormal electrocardiograms were under 40 years of age.

The group of 35 patients with abnormal electrocardiograms included one patient with clinical evidence of arteriosclerotic heart disease and two patients with clinical evidence of rheumatic heart disease. There was clinical evidence of arteriosclerosis in seven patients and of rheumatic heart disease in three patients in the entire group of 64 patients.

TABLE XVII
Electrocardiographic Findings in Addison's Disease (58 patients)

Age Group (years)	Number of Patients	Electrocardiographic Interpretation			
		Normal	"Borderline" *	Myocardial Damage †	Per Cent Abnormal
20-29	16	7	5	4	56
30-39	18	8	4	6	56
40-49	13	6	4	3	54
50-59	8	1	3	4	88
60-69	3	1	2	0	67
TOTAL	58	23	18	17	60

* The term "borderline" has been used to indicate the presence of abnormal electrocardiographic changes which are believed to be significant, although not indisputable evidence of myocardial damage. These changes were as follows: PR interval over .21 second; prolonged QT interval (by formula of Ashman and Hull²⁴); QRS voltage less than 5 mm. in Leads I, II, III and/or Lead IV F; isoelectric T₁ or T₂; negative T₄; initial upward QRS deflection in Lead IV F absent or less than 1 mm.; ST segment deviation of less than 1 mm.

† As indicated by inverted T₁ and/or T₂, isoelectric T-waves in all leads, or the presence of combinations of three or more of the "borderline" changes.

TABLE XVIII

Incidence of Electrocardiographic Changes in Addison's Disease (58 patients)

Change	Number of Patients	Per Cent
Prolonged PR interval*	12	21
Prolonged QT interval*	15	26
Low voltage (QRS)*		
Leads I, II, III	11	19
Lead IV F	9	16
Low or isoelectric		
T ₁	19	33
T ₂	19	33
T ₄	4	7
Diphasic or Negative		
T _i	5	9
T ₂	11	19
T ₃	39	67
T ₄	19	33

* See footnote to table 17.

The preponderance of females among the patients with abnormal electrocardiograms is of interest. Twenty (57 per cent) of the 35 patients with significant electrocardiographic changes were females (chart 5). Of the 26 females studied 77 per cent had abnormal electrocardiograms, whereas only 47 per cent of the males were in this group. The explanation for this

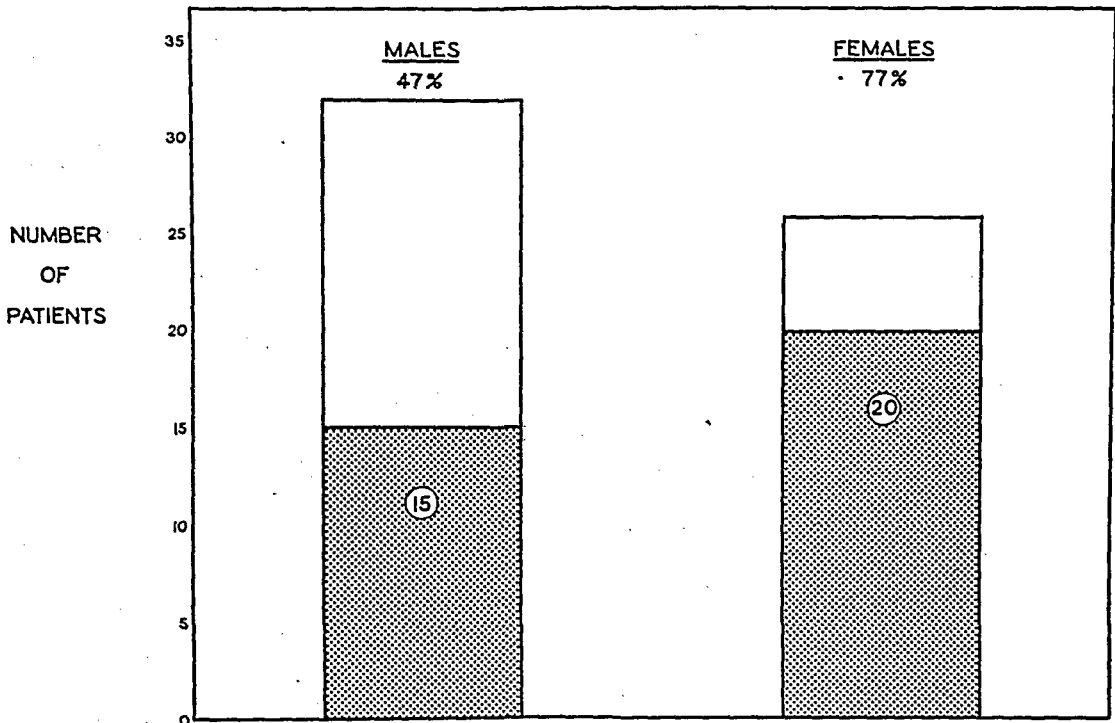


CHART 5. Electrocardiographic abnormalities in Addison's disease (sex incidence) patients with abnormal electrocardiograms.

Males: "borderline" changes—9; myocardial damage—6. Females: "borderline" changes—9; myocardial damage—11.

greater frequency of abnormal electrocardiographic changes in the females is not apparent. However, in support of this apparently higher incidence of cardiac abnormalities in female patients is the fact that five of the seven deaths which could be attributed to cardiovascular disease (entire group of 158 patients, table 12) occurred in female patients.

There appeared to be no pattern of electrocardiographic changes specific for Addison's disease. A wide variation characterized the changes, viz., prolonged PR and QT intervals, low QRS voltage, and low or inverted T-waves. The incidence of these findings in this group of patients was considerably higher than that reported recently for a normal population.^{22, 23} Other significant electrocardiographic changes observed less frequently were: an absence of the initial upward QRS deflection in the chest lead (two patients), small initial upward QRS deflection in the chest lead (seven patients), sinus bradycardia with cardiac rate of less than 50 per minute (five patients), premature ventricular contractions (four patients) and ST segment depression of less than 1 mm. (four patients).

In no instance was an electrocardiogram included in this series which had been taken during digitalis therapy or within three weeks after digitalis therapy had been discontinued. Since no attempt was made to standardize the position of patients during the recording of electrocardiograms, it is possible that in some instances inversion of T₂ actually represented a change related to the sitting position.²⁴ In no patient in this series, however, did the interpretation of myocardial damage depend solely upon the presence of inversion of T₂.

Effect of Desoxycorticosterone Therapy upon the Electrocardiogram in Addison's Disease: The relation of potassium retention to changes in the electrocardiogram has been reported in experimental adrenal insufficiency.²⁵ The abnormal electrolyte pattern is restored to normal in adrenalectomized animals and in patients with Addison's disease by desoxycorticosterone acetate therapy. Excessive desoxycorticosterone acetate therapy can produce an abnormal electrolyte pattern in both the blood serum and tissues, i.e., high sodium, low potassium.¹⁴ Presumably changes in the electrocardiogram could accompany these disturbances in electrolyte concentration. Changes in the electrocardiogram associated with low serum potassium have been observed in a patient with familial periodic paralysis.²⁶ The relation of the disturbances in electrolyte metabolism to changes in carbohydrate metabolism and cardiac function is not fully understood.

Electrocardiograms were recorded in 28 patients before desoxycorticosterone therapy was begun and repeated during therapy (1.4 years, average duration of therapy—tables 19 and 20). In 13 additional patients electrocardiograms were taken after desoxycorticosterone therapy had been begun. Of this total group of 41 patients, seven showed significant improvement in the electrocardiogram during therapy, whereas 14 showed an increase in the number and extent of the abnormalities. Five of the seven instances of

improvement were related to recovery from periods of inadequate therapy or of overdosage with hormone. In contrast, only two of the 14 instances of impairment of the electrocardiogram coincided with a period of unfavorable clinical response. The remaining 12 patients showed a moderate to marked improvement in well-being, at the time that the electrocardiogram

TABLE XIX

Changes in Electrocardiograms Which Occurred During Desoxycorticosterone Acetate Therapy (Addison's Disease)

	Number of Patients	Electrocardiographic Interpretation			
		Normal	"Border-line" *	Myocardial Damage	Per Cent Abnormal
Prior to hormone therapy	28	19	6	3	32
Following 1.4 years of continuous hormone therapy	28	12	8	8	57

* See footnote to table 17.

TABLE XX

Incidence of Electrocardiographic Changes in 28 Patients with Addison's Disease Prior to and During Desoxycorticosterone Acetate Therapy

	* Prolonged PR Interval	* Prolonged QT Interval	* Low QRS Voltage		Low or Isoelectric			Diphasic or Negative			
			I II III	IV	T ₁	T ₂	T ₄	T ₁	T ₂	T ₃	T ₄
Prior to desoxycorticosterone acetate therapy	0	2	4	2	4	2	3	0	4	11	4
During desoxycorticosterone acetate therapy (1.4 yrs.)	9	10	5	2	6	5	2	5	11	19	8

* See footnote to table 17.

was giving evidence of progressive myocardial involvement. The most striking abnormalities developing under desoxycorticosterone therapy were prolongation of the PR interval (10 patients) and prolongation of the QT interval (10 patients). No patients showed a prolonged PR interval before receiving synthetic hormone (table 20). T-wave inversion suggesting diffuse myocardial damage or coronary insufficiency appeared in six patients, three of whom had had normal and three of whom had had "borderline" electrocardiograms before treatment.

The number of patients showing myocardial damage increased from three to eight during desoxycorticosterone therapy in the group of 28 patients in whom records were available prior to treatment with synthetic hormone (table 19). No increase in the number of patients with electrocardiographic abnormalities occurred in the smaller group of 13 patients in whom records were made only during the period of desoxycorticosterone

TABLE XXI
Summary of Electrocardiographic Findings in Patients with Addison's Disease prior to and during Desoxycorticosterone Acetate Therapy

	Number of Patients	Duration of Hormone Therapy (years)	Electrocardiographic Interpretation							
			Normal		* Borderline		Myocardial Damage		Abnormalities	
			1st ECG	Present	1st ECG	Present	1st ECG	Present	1st ECG	Present
Serial electrocardiograms prior to and during hormone therapy	28	1.4	19	12	6	8	3	8	32%	57%
Serial electrocardiograms during hormone therapy (no record prior to therapy)	13	2.1	4	4	7	8	2	1	69%	69%
Single electrocardiograms prior to hormone therapy (none since)	9	0	6	—	3	—	0	—	38%	—
Single electrocardiograms during hormone therapy	8	0.8	—	5	—	1	—	2	—	38%
Total: electrocardiograms prior to hormone therapy	37	—	25	—	9	—	3	—	32%	—
Total: electrocardiograms during hormone therapy	49	1.5	—	21	—	17	—	11	—	57%

*See footnote to table 17.

therapy (table 21). This difference in the two groups did not appear to be related to the duration of Addison's disease or to the clinical response to therapy, but may indicate that electrocardiographic abnormalities make their appearance early during the period of rapid clinical improvement which follows the *initiation* of desoxycorticosterone therapy. It is possible that in untreated patients myocardial disease may be masked by the decreased demands made on the heart by the lowered arterial pressure and reduced blood volume of patients in adrenal insufficiency. By elevating blood pressure and restoring blood volume, desoxycorticosterone therapy disturbs this balance, increases the cardiac load, and may thereby lead to electrocardiographic abnormalities in patients with latent myocardial damage.

Electroencephalographic Changes in Addison's Disease: Electroencephalograms* were recorded in 36 of the 64 patients under our observation. Definite abnormalities were noted in 25 or 69 per cent of these 36 patients. The abnormal features in most instances consisted of one or more of the following changes:

- (1) regular occurrence of oscillations slower than the normal alpha rhythm with a predilection for the frontal areas, not influenced by opening the eyes.

- (2) absence of, or greatly decreased number of low voltage, fast frequency waves (beta waves).

- (3) increased sensitivity to hyperventilation.

Unfortunately in the majority of patients it was not possible to obtain electroencephalographic records prior to synthetic hormone therapy. However, in two of the three patients who were studied before therapy had been instituted, changes similar to those noted above were observed. The effect of desoxycorticosterone therapy on the electroencephalographic records was unpredictable. Four patients with normal electroencephalograms, early in the course of therapy, also had normal tracings after 4 to 27 months of continued hormone therapy. Four patients with abnormalities in the electroencephalograms early in the course of synthetic hormone therapy showed no progression of the abnormal changes during the subsequent 12 months of treatment. Three patients, however, showed a pronounced increase in the abnormal electroencephalographic features during a 12 month period of desoxycorticosterone acetate treatment. In contrast to these evidences of progressive change in the resting pattern of the electroencephalogram during hormone therapy, four patients were observed to have a pronounced decrease in the abnormal sensitivity to hyperventilation during a 12 month period of synthetic hormone therapy.

The situation in relation to the changes in the electroencephalogram of patients with Addison's disease treated with desoxycorticosterone acetate is

* We are greatly indebted to Dr. W. Christie Hoffmann of the Henry Phipps Psychiatric Clinic for the encephalographic records. A complete study of the electroencephalographic changes in these patients has been prepared for publication.²⁷

somewhat analogous to that which was observed in relation to the abnormal electrocardiographic changes in the same group of patients. In both instances typical abnormalities were present before synthetic hormone therapy was instituted, and in most instances continued synthetic hormone therapy failed to correct the abnormalities despite striking evidence of clinical improvement. Although in both instances it was thought likely that the extensive and progressive changes in electrocardiogram and electroencephalogram might be correlated with the degree to which carbohydrate metabolism was impaired in these patients, such a correlation was not present in all cases. A higher incidence of abnormal electroencephalograms was noted in male patients in contrast to the predominance of abnormal electrocardiograms which was observed in female patients.

METABOLIC STUDIES

A. Plasma Electrolytes and Plasma Volume: A striking increase in plasma volume is one of the first changes which is noted in patients with Addison's disease under desoxycorticosterone acetate treatment.² If not measured directly, some idea of the magnitude of the increase in plasma volume can be obtained from the changes in hematocrit, red blood cell count and serum protein concentration which occur during the first few days of therapy. In addition to the prompt increase in plasma volume there is also a restoration of the plasma concentration of sodium, chloride, potassium and non-protein nitrogen to normal levels. During treatment with synthetic hormone the renal excretion of sodium and chloride is decreased (positive balance), whereas the excretion of potassium and inorganic phosphorus is increased (negative balance). Withdrawal of hormone therapy is followed rapidly by increased excretion of sodium, chloride and water, weight loss, decrease in plasma volume, decrease in *total plasma content* of sodium and chloride, retention of potassium and inorganic phosphorus associated with an increase in the concentration of potassium in plasma.² Patients may improve remarkably during the early period of therapy without necessarily showing any increase in plasma concentration of sodium and chloride; ultimately, however, these values attain normal levels. Conversely, sudden withdrawal of hormone therapy may temporarily precipitate a crisis without necessarily effecting a significant reduction in the concentration of sodium and chloride in the plasma. This apparent lack of correlation between changes in clinical state and changes in plasma concentration of electrolytes can be understood if plasma volume measurements are made during these periods, since it can be readily demonstrated that during the early period of treatment there is an appreciable *increase in the total plasma content of sodium and chloride* and that immediately following withdrawal of therapy there is a *reduction in the total plasma content of these ions*. Whether or not corresponding changes take place in the plasma concentration of these ions depends upon the relative gain or loss of water.

The changes which occurred in blood sugar and non-protein nitrogen levels, as well as plasma sodium, potassium, chloride and carbon dioxide combining power, hematocrit and serum protein concentration during desoxycorticosterone acetate in 44 of our 64 patients are summarized in table 22. It is of particular interest to note that the fasting blood sugar level

TABLE XXII

Blood Chemical Changes in Patients with Addison's Disease During Desoxycorticosterone Acetate Therapy

Number of Patients	Blood Chemical Constituent	Mean Value Prior to Therapy	Mean Value during Therapy	Difference Between Means *
				Standard Deviation of the Distribution of the Means
40	Serum sodium m.eq./l.	132.3	141.3	4.5
41	Serum chloride m.eq./l.	97.5	104.3	4.2
38	Carbon-dioxide combining capacity	24.2	26.0	2.9
44	Serum potassium m.eq./l.	5.7	4.4	5.0
42	Non-protein nitrogen mg./100 c.c.	34	28	3.6
42	Blood sugar mg./100 c.c.	87	81	2.7
42	Hematocrit (per cent cell volume)	41.4	36.5	4.5
37	Serum protein gm./100 c.c.	6.3	5.7	3.7

* The difference between means is significant when the value of this factor is greater than 2.

$$\sqrt{\frac{\sigma_o^2}{N}}$$

Standard deviation of the distribution of means of individual changes.

N = Number in series

$\sigma_o = \sqrt{\frac{(X_1 - X_2)^2}{N}}$ = Standard deviation of the distribution of individual changes

$(X_1 - X_2)^2$ = Sum of squares of difference in means in series 1 and 2 (the two series being compared)

N = number in series

\bar{X}_1 = Mean of series 1

\bar{X}_2 = Means of series 2

If $\frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{\sigma_o^2}{N}}} > 2$, difference of $\bar{X}_1 - \bar{X}_2$ is significant.

(Note that N occurs in this formula twice—once as a part of γ_o^2 .)

prior to desoxycorticosterone acetate therapy was significantly higher than during therapy. This suggests that not only does desoxycorticosterone acetate lack the carbohydrate-stimulating quality of certain adrenal cortical steroids, but that it may actually exert a slight insulin-like action. The changes in serum electrolyte concentration which occurred during synthetic hormone therapy were significant and were consistent with the changes reported previously.²

B. Basal Metabolic Rate: In an earlier report¹¹ it was shown that a basal metabolic rate of less than —20 per cent of standard was unusual in

patients with Addison's disease uncomplicated by thyroid or pituitary deficiency. Furthermore, it was shown that in a group of seven patients no significant change in basal metabolic rate was noted following continued treatment with desoxycorticosterone acetate, the average value before treatment being — 10 per cent (18 determinations) and during treatment — 12 per cent (10 determinations). The basal metabolic rates of 55 of the 64 patients in the Johns Hopkins Hospital group have been measured on several

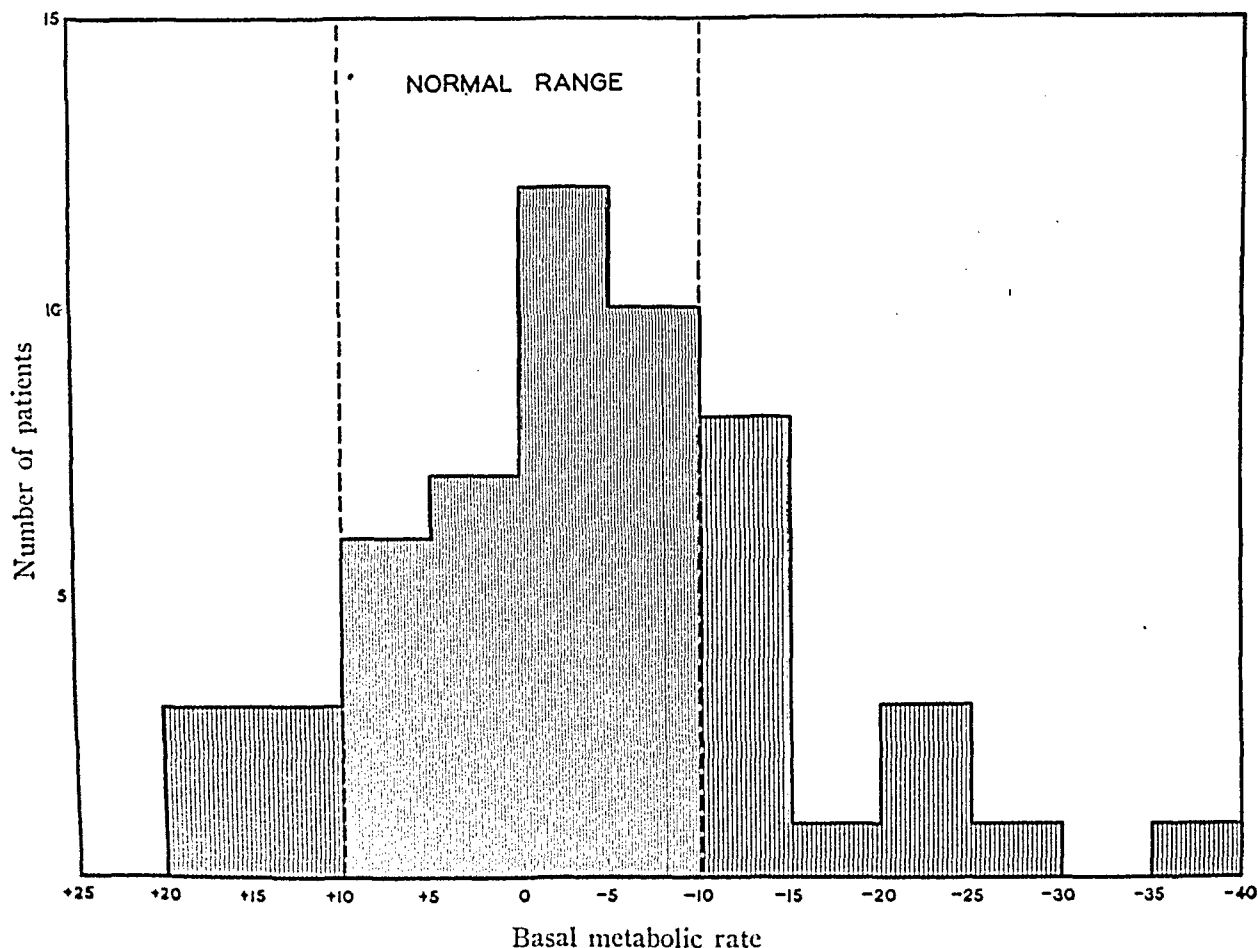


CHART 6. Basal metabolic rate in fifty-five patients with Addison's disease (Johns Hopkins Hospital) during treatment with desoxycorticosterone acetate.

occasions during desoxycorticosterone acetate therapy. The average value of these determinations for each patient is presented in chart 6. It is to be noted that the values for 35 patients or 64 per cent of the group lie between + 10 per cent and — 10 per cent of standard. In six patients the values exceeded + 10 per cent and in 14 patients the values were below — 10 per cent, five of the latter being below — 20 per cent. All five of this latter group presented definite clinical evidence of thyroid deficiency.

C. Pigmentation: Abnormal pigmentation was present in 60 (94 per cent) of the 64 patients in our group. Vitiligo was present in eight, or 13 per cent, of these 60 patients. The occurrence of vitiligo in the presence of

adrenal cortical deficiency was pointed out by Addison in his original monograph.⁷

In considering the type of abnormal pigmentation which may occur in patients with Addison's disease it may be helpful to list the variety of changes which have been observed in the present group of patients, viz.:

1. Bluish-black discolorations which appear on the lips, gums and on the mucous membranes of the mouth, rectum and vagina. It should be pointed out that this type of pigmentation occurs normally in negroes and in certain southern European races.

2. A diffuse tan over the non-exposed as well as the exposed portions of the body.

3. Hyperpigmentation of the extensor surfaces of the body, pressure points, scars and lines on the palms of the hands.

4. Multiple black freckles, distributed most commonly over the forehead, face, neck, shoulders and arms.

5. Areas of vitiligo or leukoderma. The appearance of these areas is usually striking because of the hyperpigmentation of the surrounding skin.

It is not possible to predict what change, if any, may occur in the pigmentation of patients with Addison's disease during treatment with desoxycorticosterone acetate. In all patients there is a noticeable lightening of the complexion within a few days after hormone therapy is instituted. This immediate change reflects the hemodilution and increase in peripheral circulation which has occurred as a result of sodium, chloride and water retention, increase in plasma volume and increase in blood pressure. During periods of insufficient therapy patients rapidly assume a much darker complexion.

In the majority of patients during long continued hormone therapy there has been some decrease in the intensity of the abnormal pigmentation (table 23) and in a few patients there has been complete disappearance of small localized areas of increased pigmentation. In two patients, despite continued hormone therapy, there has been a slow but progressive increase in pigmentation.

It is well known that the margins of scars which occur in patients with Addison's disease are a frequent site for increased pigment deposition. For this reason the small scars which are made in the infrascapular region during the implantation of pellets may provide an excellent indicator of the change in pigment metabolism which occurs during therapy. A striking pigmentation of the margins of these scars following the implantation of pellets of desoxycorticosterone acetate strongly suggests that the abnormality in pigment metabolism has not been corrected by synthetic hormone therapy, whereas failure of the margins of these scars to become pigmented suggests that the progress of the abnormal process has been arrested.

D. Creatine Metabolism: The presence of spontaneous creatinuria associated with a decrease in creatine tolerance has been observed in untreated

patients with Addison's disease.^{7, 28} Treatment with whole adrenal cortex extract was followed by improved appetite, increased ingestion of food, gain in weight and improved clinical condition. Under these circumstances spontaneous creatinuria disappeared and creatine tolerance improved.²⁹ It was not known whether the beneficial effect of adrenal cortex extract represented a specific effect of certain adrenal steroids on phosphocreatine metabolism or whether the improvement was merely a reflection of the improved nutritional state induced by hormone therapy.

TABLE XXIII

Changes in Pigmentation Which Occurred in 64 Patients (Johns Hopkins Hospital) with Addison's Disease during Desoxycorticosterone Acetate Therapy

	Number of Patients	Per Cent of Total of 64 Patients
Abnormal pigmentation	60	94
Vitiligo	8	13
No significant change in pigmentation during therapy	33	52
Definite decrease in pigmentation	25*	40
Complete restoration to normal	0	0
Increase in pigmentation	1	2
First appearance of pigmentation during therapy	1	2

* Six patients in this group exhibited a striking decrease in pigmentation as a result of a marked increase in the extension of the areas of vitiligo.

With the exception of one patient (A. H., chart 7), it was not possible to study the disturbance in creatine metabolism prior to the institution of desoxycorticosterone acetate therapy. The status of creatine metabolism in 15 patients, however, was investigated at a later date (following one year of continuous synthetic hormone therapy). In seven of the 16 patients (44 per cent) spontaneous creatinuria of more than 100 mg. per day was observed at this time. (The patients were maintained on a creatine-low diet during these tests.) The nutritional state and appetite of the patients at the time of these observations were good. Retention of administered creatine (chart 7) was definitely impaired in 10 of the 16 patients or 63 per cent during synthetic hormone therapy, as well as in patient A. H., prior to the institution of therapy (chart 7).

It is evident from these data that creatine metabolism was abnormal during synthetic hormone therapy in a high proportion of the patients who were tested. There was no indication that prolonged treatment resulted in progressive improvement in creatine metabolism. In two patients who received long continued therapy with adrenal cortex extract (5 to 10 c.c. daily) a high normal retention of administered creatine (97.0 and 94.9 per cent respectively) was noted.

It appears probable that the abnormality in creatine metabolism which occurs in patients with Addison's disease is aggravated by anorexia and

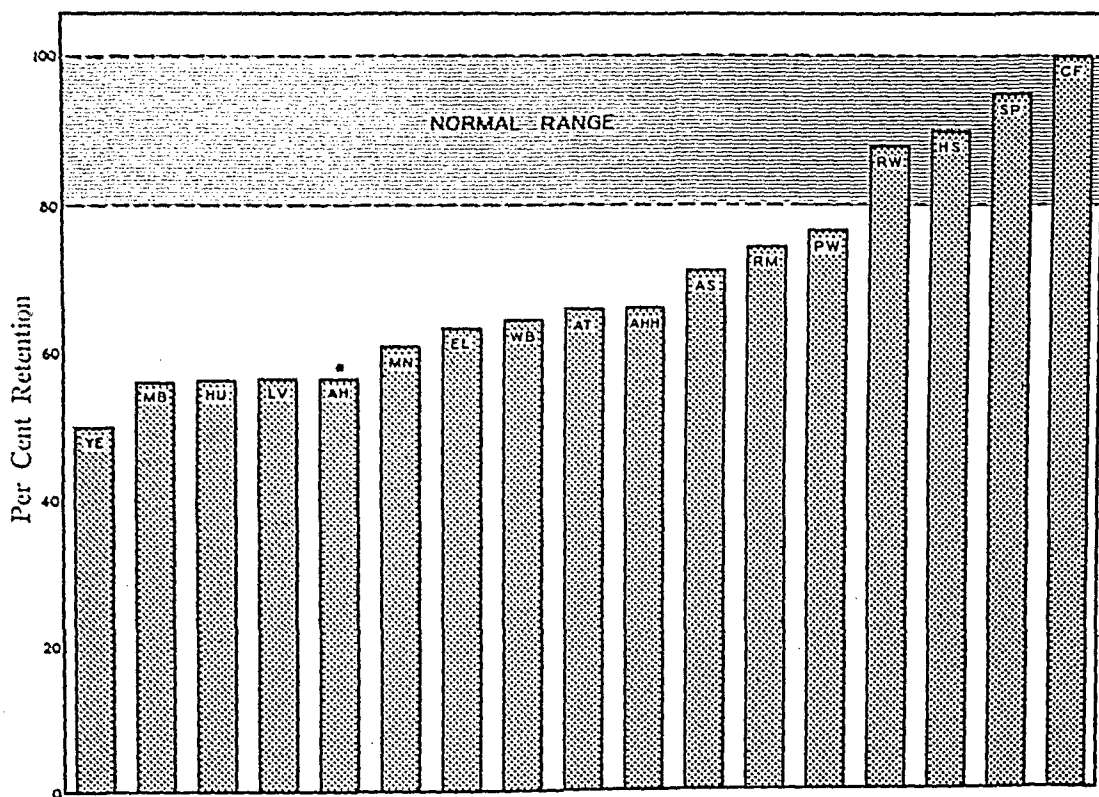


CHART 7. Creatine tolerance test * in patients with Addison's disease treated with desoxycorticosterone acetate. Creatine retention following test dose 2.64 gm.

inanutition but is certainly not dependent upon these factors. Desoxycorticosterone acetate therapy does not correct the abnormality in creatine metabolism, whereas earlier studies^{28, 29} and the studies on two patients in the present series suggest that treatment with adequate quantities of whole adrenal cortex extract may correct the underlying disturbance in creatine metabolism.

E. Renal Function: Renal function may be temporarily reduced during adrenal crisis as a consequence of reduced blood volume and reduced blood pressure. At this time there may occur a rise in blood non-protein nitrogen. Treatment with adrenal cortex extract or synthetic desoxycorticosterone acetate is followed by a rapid improvement in renal function.

One practical difficulty which arises in carrying out renal function tests in patients with Addison's disease is the inability in many instances to obtain a satisfactory rate of urine formation. This may result from the fact that these patients frequently experience considerable difficulty in ingesting large quantities of water, and furthermore, the absorption of water from the intestinal tract may occur at a rate slower than normal.

* Patients were maintained on a diet of low creatine content for a period of at least 72 hours prior to these determinations. On the day of the creatine tolerance test 2.64 gm. of creatine were administered by mouth. Details of the test and the technical methods employed have been described elsewhere.³⁰

Patient A. H. was tested prior to the institution of therapy.

A summary of the results of the phenolsulphonphthalein and urea clearance tests in 55 of the 64 patients in our group is presented in table 24. Inulin and diodrast clearances were not measured in these patients. Talbott, recently, has made a number of very careful observations on the status of renal function in patients with Addison's disease.³¹ He has demonstrated that although the phenolsulphonphthalein excretion and urea clearance may appear to be normal, more exact methods frequently demonstrate an appreciable degree of renal insufficiency.

TABLE XXIV

Summary of Renal Function Tests in 55 Patients with Addison's Disease Treated with Desoxycorticosterone Acetate (Johns Hopkins Hospital)

Phenolsulphonphthalein Test

	Number of Patients	Per Cent of Total of 55 Patients
Less than 40% excretion in 1 hour	5	9
Less than 60% excretion in 2 hours	9	16
<i>Urea Clearance</i>		
Less than 60% standard clearance	3	5

F. Hepatic Function: It is well known that the tolerance of adrenalectomized animals and patients with Addison's disease to various toxic agents is greatly reduced. One theory regarding the action of adrenal cortical hormone postulates that an important function of this hormone is its ability to assist the body in processes involving the detoxification of noxious substances.³²

Rowntree and Snell⁷ investigated hepatic function in patients with Addison's disease by studying the bilirubin content of the serum and retention of bromsulphthalein. The serum bilirubin level was uniformly normal, but the results of the bromsulphthalein test suggested slight impairment of liver function. We have studied the excretion of hippuric acid after intravenous injection of a standard dose of sodium benzoate in nine patients with Addison's disease during treatment with desoxycorticosterone acetate. In all instances the values obtained were distinctly below those observed in normal subjects (chart 8). It is of interest that four of the nine patients showed moderate splenomegaly. In no instance was there evidence of impaired renal function. It is possible that the impaired conversion of sodium benzoate to hippuric acid may reflect a defect in hepatic function occasioned by prolonged glycogen depletion or may be the result of impaired amino acid metabolism (glycine).

Intercurrent Infections: In the group of 64 patients treated in the Johns Hopkins Hospital, intercurrent infections played a significant rôle (a) as a precipitating factor in the original episode of adrenal insufficiency, (b) as a complication in the course of subsequent hormone therapy, and (c) as one of the chief causes of death. Ten patients definitely dated the onset of Addi-

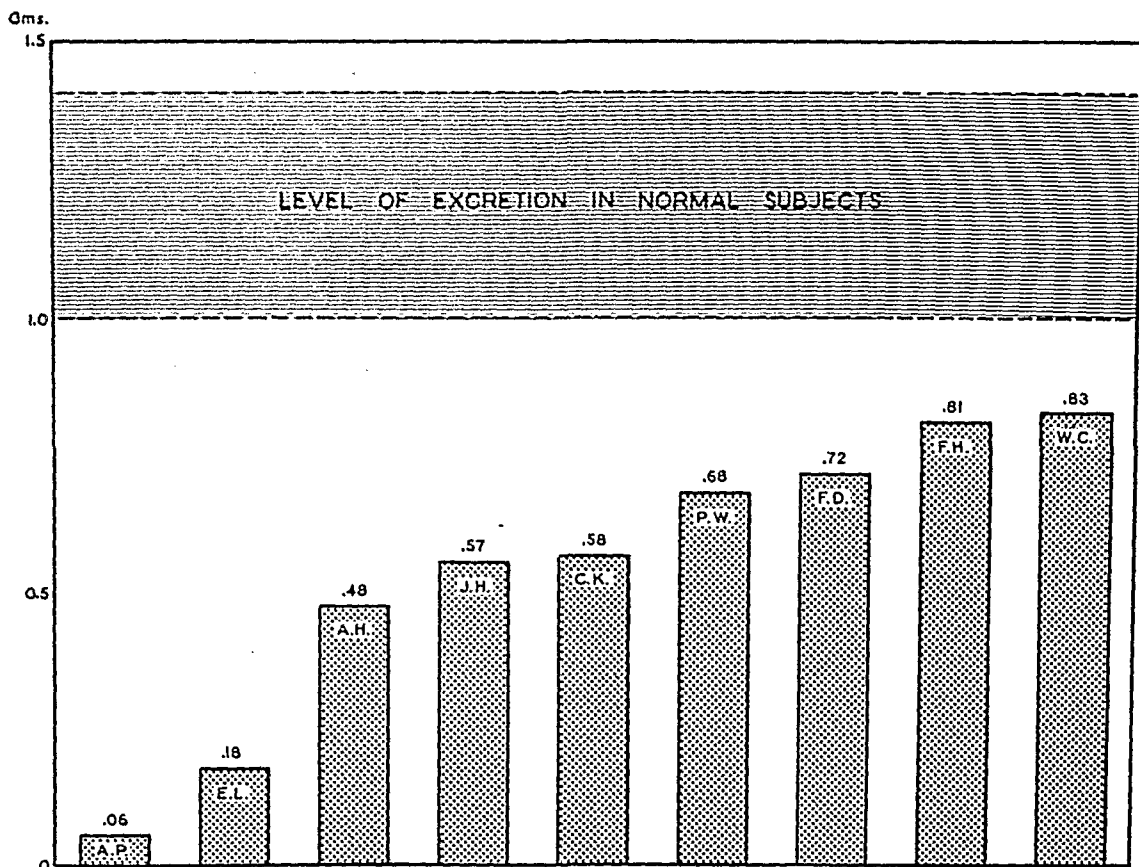


CHART 8. Hippuric acid excretion in patients with Addison's disease treated with desoxycorticosterone acetate. Excretion of hippuric acid patients.

son's disease to an acute febrile episode which was diagnosed in eight cases as "influenza," in one case as scarlet fever, and in one case as infectious mononucleosis. Exacerbation of adrenal insufficiency following acute infections occurred in 16 of the patients during treatment with synthetic hormone. In several of these patients repeated exacerbations of the disease occurred with successive bouts of infection. In five of the patients (8 per cent) crises induced by acute infections led to death. Infections due to hemolytic streptococci were one of the most common types encountered.

A striking characteristic of the response of patients with Addison's disease to acute infections was the extreme rapidity with which they became prostrate. On several occasions severe adrenal crisis with shock occurred within 48 hours of the onset of the acute infection. The increase in hormone requirement was very great during this period. Thus the problem of immediate and intensive early treatment had to be met. It is to be noted that although patients treated with synthetic hormone may experience a crisis induced by an acute intercurrent infection, the convalescence of these patients is very rapid in comparison with the prolonged period of invalidism previously observed in patients with Addison's disease.

Extremely encouraging results have been obtained recently in two patients with acute hemolytic streptococcus infection in which *sulfadiazine* was used in conjunction with adrenal cortex extract, desoxycorticosterone acetate and intravenous infusion of sodium chloride and glucose solution.¹³ Sulfadiazine appears to be the most desirable of the sulfonamide drugs in treating patients with Addison's disease because of the low incidence of nausea and vomiting associated with its administration. The basic routine treatment which was employed in these two patients is similar in every respect to that outlined in "the treatment of adrenal crisis," the only difference being the addition of sulfadiazine therapy. An initial dose of 4 to 5 gm. of the sodium salt was given intravenously in conjunction with the infusion of saline and glucose solutions as soon as the patient was seen. Subsequently 1 gm. of sulfadiazine was given by mouth every four to six hours and an attempt was made to maintain a blood level of 10 to 20 mg. per 100 c.c. as long as fever persisted. In the event that sulfadiazine could not be taken by mouth, the intravenous injection of sodium salt of sulfadiazine (2 gm.) was repeated at 8 to 12 hour intervals. The importance of administering large quantities of adrenal cortex extract at frequent intervals, in conjunction with saline and glucose infusions and a supplementary dose of desoxycorticosterone acetate has been pointed out. The prompt recognition of infections and the appreciation of the necessity for immediate hospitalization with intensive therapy should do much toward reducing the relatively high mortality rate from hemolytic streptococcus infections in patients with Addison's disease. It is apparent that the hormone requirement of patients who have recently experienced an acute infection may be temporarily and even permanently increased.

Effect of Pregnancy: In one patient (H. B.) signs of adrenal insufficiency became manifest during pregnancy. In two other patients (K.D., and M.P.) an increase in pigmentation which was not considered to be beyond normal was noted during pregnancy. However, following the termination of pregnancy, the pigmentation in these two patients became progressively more intense instead of diminishing. In two patients (R. G., and M. P.) the first episode of adrenal crisis was precipitated by delivery. In one patient (A. K.) interruption of pregnancy was followed by septicemia and death. At present one patient (K. D.) is again pregnant.

The early weeks of pregnancy are especially difficult for patients with Addison's disease because of the associated nausea and vomiting. During this period it may be necessary to supplement desoxycorticosterone acetate treatment with daily injections of adrenal cortex extract and infusions of saline and glucose. The latter months of pregnancy should be rather well tolerated because of the sodium-retaining effect of the sex hormones,²³ and the secretion of the fetal adrenal. It has been demonstrated repeatedly that the hormone requirement of adrenalectomized animals is greatly reduced during pregnancy,^{24,25} and the beneficial effect of progesterone on the life

maintenance of adrenalectomized animals is well known.³⁶ Desoxycorticosterone acetate treatment during the latter months of pregnancy should be regulated carefully to prevent excessive sodium and chloride retention.

The period immediately following delivery may prove to be a very critical one for patients with Addison's disease. Blood loss, the removal of supplementary adrenal cortical hormone provided by the fetus and the rapid decrease in titer of sex hormones may readily induce a crisis. Collapse at the time of delivery may result in hemorrhage into the anterior pituitary with resulting pituitary deficiency.³⁷ Therefore, patients with Addison's disease should be treated for impending crisis immediately prior to delivery (see section on preoperative therapy).

Although pregnancy is distinctly contraindicated in patients with Addison's disease, once established, it is probably much safer to attempt to carry the pregnancy to termination unless very unusual complications supervene. The need for hospitalization and careful supervision at the time of delivery should be emphasized.

Surgery in Addison's Disease: Patients with Addison's disease have long been known to represent extremely poor surgical risks.⁷ Minor operative procedures such as dental extractions have been known to precipitate a crisis, and major operative procedures frequently resulted in death. Several factors contribute to the poor response of patients with Addison's disease to surgical procedures:

1. Lowered tolerance to narcotics and anesthetics.
2. Hypotension.
3. Dehydration and reduced plasma volume.
4. Depleted carbohydrate reserves.
5. Myocardial damage.

The first four of these disturbing factors may be corrected by adequate treatment with adrenal cortex extract, desoxycorticosterone acetate and intravenous infusions of saline and glucose solutions. At present with the improved management of patients it is possible to carry patients successfully through major operative procedures. A comparison has been made between the effect of surgery on patients prior to therapy (and in some instances prior to the diagnosis of Addison's disease) and subsequently (table 25). All seven patients did very poorly following operative procedures which were carried on prior to specific therapy. In five of these seven patients it appeared that the operative procedure hastened the development of the classical clinical picture of the disease (table 25, Section A). Of the seven treated patients (table 25, Section B), six had an uneventful postoperative course with the exception, in one patient, of a rather mild hypoglycemic episode during the second postoperative day. The seventh patient died on the forty-first postoperative day following a therapeutic abortion complicated by perforation of the uterus, pelvic vein thrombophlebitis, mul-

TABLE XXV

Complications of Surgical Operations in Patients with Addison's Disease

A.

Patient	Sex	Present Age	Operation	Hormone Therapy	Remarks
F. H.	M	24	Appendectomy	0	Precipitated adrenal crisis.
R. G.	F	28	Hysterectomy	0	Crisis, onset of Addison's disease.
R. M.	F	36	Tonsillectomy	0	Crisis, onset of Addison's disease.
E. V.	M	43	Cholecystectomy	0	Stormy postoperative period, onset of Addison's disease.
A. H.	F	40	Dental extraction	0	Crisis.
H. S.	M	49	Tonsillectomy	0	Stormy postoperative period, onset of Addison's disease.
A. S.	F	46	Hysterectomy	0	Prolonged convalescence, onset of Addison's disease.

B.

D. B.	M	36	Herniorrhaphy	Desoxycorticosterone acetate	Uneventful convalescence.
E. F.	F	50	Dental extraction	Desoxycorticosterone acetate	No complications.
F. H.	M	24	Tonsillectomy	Desoxycorticosterone acetate+adrenal cortex extract.	Uneventful convalescence.
A. H.	F	41	Hemorrhoidectomy	Desoxycorticosterone acetate+adrenal cortex extract.	Uneventful convalescence.
A. K.	F	32	Therapeutic abortion	Desoxycorticosterone acetate	Septicemia, death.
F. G.	F	32	Appendectomy	Desoxycorticosterone acetate.	Uneventful convalescence.
J. P.	M	22	Nephrectomy	Desoxycorticosterone acetate+adrenal cortical extract.	Immediate postoperative course excellent, late convalescence complicated by excessive sodium retention, present health excellent.
A. S.	M	35	Epididymectomy	Desoxycorticosterone acetate+adrenal cortex extract.	Uneventful convalescence.

multiple pulmonary infarcts, severe pyelitis and *B. coli* bacteremia. It is of interest to note that this patient's blood pressure was maintained at a level of 125 mm. Hg systolic and 80 mm. diastolic until shortly before death.

Technic for Preparing Patients with Addison's Disease for Surgery: Local anesthesia is used whenever possible. When necessary a general anesthetic may be used, but care should be taken not to use anesthetic agents which induce an appreciable degree of anoxia. The ideal general anesthetic for patients with Addison's disease is yet to be discovered. It is possible that cyclopropane may prove to be the best for these patients. Cyclopropane

has been used successfully, although the undesirable features of using this anesthetic in general operating rooms is well known. Pre-anesthetic morphine is given in reduced dosage, i.e., 5 to 10 mg. instead of 10 to 15 mg. It is our custom to give adrenal cortex extract and desoxycorticosterone acetate in increased doses for 24 to 48 hours prior to operation in an effort to increase liver glycogen, plasma volume and blood pressure. Adrenal cortex extract, 5 c.c. every four hours day and night for 48 hours preceding operation and 10 mg. of desoxycorticosterone acetate, once daily, is a safe routine. Early on the morning of operation, an intravenous infusion of 1000 c.c. of sodium chloride, 0.9 per cent, and glucose, 5 to 10 per cent, is given as well as a supplementary dose of 10 to 15 c.c. of adrenal cortex extract and 10 mg. of desoxycorticosterone acetate. A second infusion of saline and glucose is instituted at the time that the anesthetic is started, and 25 c.c. of adrenal cortex extract are added directly to the infusion. Additional extract is given during the operation if the systolic blood pressure falls below 120 mm. Hg. Epinephrine is given immediately (0.5 c.c.) subcutaneously if the systolic blood pressure falls below 100 mm. Hg. Following operation the patient is treated in a manner similar to that described under "treatment of adrenal crisis." Care should be taken not to give large doses of desoxycorticosterone acetate when the fluid requirement during the postoperative period is being provided by saline and glucose infusions.

DISCUSSION

An analysis of the etiological factors responsible for adrenal cortical insufficiency in this group of 158 patients suggests that the incidence of tuberculosis is appreciably lower than that previously reported. This fact is of significance in relation to the therapeutic response which may be expected, since patients with active tuberculosis or extensive, healed tuberculosis present complications which are not encountered in the non-tuberculous group.

There is no evidence to show that a daily intramuscular injection of synthetic hormone in oil regularly taken is inferior to pellet therapy except in relation to the quantity of hormone which is required. However, the implantation of pellets of crystalline hormone has definite advantages in the treatment of patients who are unable or unwilling to coöperate by continuing daily injections of hormone indefinitely. Sublingual administration of hormone is not practical in most instances because hormone must be taken frequently throughout the day (four to six times daily) and relatively large quantities of hormone are required, hence the cost of therapy is excessively high.

The results of therapy in the present group of patients are striking as judged by survival at 1.5 years and by the extent to which these patients have been rehabilitated. However, it must be pointed out that the present good state of the majority of these patients is the result of intensive therapy with synthetic hormone, supplemented in crisis or during the course of intercurrent infections with adrenal cortex extract therapy and parenteral

TABLE XXVI

Summary of Observations on 64 Patients Treated with Desoxycorticosterone Acetate

Patient	Sex & Age	Occupation	Etiology of Addison's Disease	Duration of Disease (years)	Complications	Blood Pressure		Body Weight		Duration of Hormone Therapy (years)	Carbohydrate Defect	Electroencephalogram	Electrocardiogram	Present Therapy			Present Condition †
						* Admission	Present	* Admission	Present					Desoxycorticosterone Acetate	Added Sodium Chloride gm.	Adrenal Cortex Extract	
M. A.	48	Housewife	Tuberculous	14.0	Preexisting hypertension	136/84	133/86	55.0	58.9	0.4	—	—	"Borderline"	Pellets	3	0	A
F. B.	48	Housewife	Non-tuberculous	7.0	Cirrhosis, arthritis	110/74	180/110	48.0	50.0	2.8	0	—	Normal	Pellets	9	0	C
F. B.	48	Housewife	Non-tuberculous	7.0	Rheumatic heart disease	100/70	130/80	53.0	60.0	0.3	++	—	—	Pellets	0	0	D
M. B.	48	Clerk	Non-tuberculous	3.0	None	100/75	140/80	45.5	56.0	0.7	—	Abnormal	Normal	Pellets	0	0	A
F. B.	41	Housewife	Non-tuberculous	3.0	Arthritis, anemia	90/60	150/100	47.3	42.2	1.3	0	—	"Borderline"	Pellets	0	0	B
M. B.	41	Clerk	Non-tuberculous	4.0	Hypothyroidism	92/74	150/112	41.5	50.9	2.6	++	Abnormal	Myocardial damage	Pellets	3	0	A
F. B.	41	Housewife	Non-tuberculous	9.0	None	105/70	118/80	60.0	60.5	2.3	—	Normal	—	Pellets	0	0	A
F. B.	41	Teacher	Non-tuberculous	5.0	Hypothyroidism, anemia	90/66	102/60	49.4	52.9	1.0	++	—	"Borderline"	Pellets	0	0	D
M. B.	42	Salesman	Non-tuberculous	4.0	None	120/76	120/70	56.3	60.5	1.7	++	—	Normal	Pellets	2	0	A
D. B.	42	Printer	Non-tuberculous	4.0	Inguinal hernia	108/70	168/98	64.7	68.6	2.9	++	—	Normal	Pellets	6	0	A
F. B.	43	Engineer	Non-tuberculous	2.0	None	96/82	150/92	60.0	88.6	0.8	—	—	—	Pellets	2	0	A
M. B.	43	Truckdriver	Non-tuberculous	4.0	None	80/50	112/82	50.0	56.0	1.1	++	Abnormal	Normal	Pellets	5	0	A
M. B.	43	Housewife	Non-tuberculous	4.0	Anxiety neurosis	124/76	118/74	43.1	44.5	2.4	0	—	Normal	Pellets	0	5 c.c.	B
F. B.	43	Unemployed	Non-tuberculous	8.0	Hypothyroidism	98/60	130/82	64.1	72.8	1.3	++	Abnormal	"Borderline"	Pellets	0	0	C
F. B.	49	Housewife	Non-tuberculous	2.0	Pregnancy	105/60	115/65	38.8	40.9	1.3	++	Normal	Normal	Pellets	5	0	A
M. B.	49	Writer	Non-tuberculous	5.0	None	96/58	108/70	66.8	66.4	3.0	++	Abnormal	Normal	Pellets	5	0	A
F. B.	49	Clerk	Non-tuberculous	3.0	None	80/60	116/78	50.1	66.6	2.8	++	Abnormal	"Borderline"	Pellets	0	0	B
M. B.	49	Unemployed	Non-tuberculous	2.0	Arthritis	108/70	120/80	62.5	69.0	0.2	—	—	"Borderline"	Pellets	10	0	D
F. B.	59	Mail Carrier	Non-tuberculous	6.0	Arteriosclerosis, senility	104/78	132/78	51.2	48.0	1.7	0	—	"Borderline"	Pellets	8	0	D
F. B.	59	Housewife	Non-tuberculous	4.0	Rheumatic heart disease	102/74	105/65	51.9	56.4	2.6	++	—	"Borderline"	Pellets	0	0	B
F. B.	61	Mechanic	Tuberculous	3.0	Active tuberculosis	90/60	120/80	55.9	68.2	1.2	++	—	Normal	Pellets	0	3 c.c.	B
M. B.	61	Student	Non-tuberculous	1.0	Active tuberculosis	80/60	140/100	68.2	72.3	0.3	++	Abnormal	Normal	Pellets	0	0	A
F. B.	49	Housewife	Non-tuberculous	2.0	Arthritis	90/50	142/98	78.2	59.6	1.3	—	Normal	"Borderline"	Pellets	3	0	B
F. B.	52	Teacher	Non-tuberculous	2.0	Hypothyroidism	107/60	120/80	38.3	46.0	1.5	++	Abnormal	Myocardial damage	Pellets	3	0	B
M. B.	52	Mechanic	Tuberculous	1.0	Healed pulmonary tbc.	105/70	122/76	88.1	87.3	0.3	++	Abnormal	Normal	Pellets	1	0	A
F. B.	30	Clerk	Non-tuberculous	3.0	None	104/65	110/70	46.8	47.7	2.6	++	Abnormal	"Borderline"	Pellets	0	0	A
F. B.	51	Housewife	Tuberculous	6.0	Anemia	116/70	135/78	44.9	54.7	1.2	+	—	Myocardial damage	Pellets	5	0	A
F. B.	52	Clerk	Non-tuberculous	4.0	None	100/60	110/65	63.2	68.2	2.9	++	Abnormal	Normal	Pellets	5	0	A
M. B.	52	Clerk	Non-tuberculous	3.0	Splenomegaly	95/54	150/100	59.5	66.4	2.3	++	Abnormal	"Borderline"	Pellets	0	5 c.c.	A
F. B.	54	Housewife	Tuberculous	3.0	Active tuberculosis	108/76	120/88	58.1	59.1	1.8	0	Abnormal	Myocardial damage	Pellets	3	0	A
F. B.	54	Housewife	Non-tuberculous	4.0	None	90/60	120/80	45.0	47.3	1.1	0	Normal	Myocardial damage	Pellets	0	0	A
F. B.	36	Teacher	Tuberculous	5.0	None	108/70	107/70	53.0	53.0	2.3	++	Abnormal	Normal	Pellets	3	0	B
F. B.	36	Housewife	Non-tuberculous	5.0	Splenomegaly	90/58	118/76	40.0	44.9	2.5	++	Abnormal	Myocardial damage	Pellets	3	0	B
M. B.	38	Salesman	Non-tuberculous	1.0	None	120/74	120/78	80.5	85.0	0.6	—	—	Normal	Pellets	0	0	D
M. B.	45	Service Mgr.	Tuberculous	7.0	Active tuberculosis	80/60	130/90	65.6	76.0	1.5	+	Abnormal	Myocardial damage	Pellets	0	0	B

TABLE XXVI—Continued

Patient	Sex	Age	Etiology of Addison's Disease	Duration of Disease (years)	Complications	Blood Pressure		Body Weight		Duration of Hormone Therapy (years)	Carbohydrate Defect	Electroencephalogram	Electrocardiogram	Present Therapy			Present Condition
						* Admission	Present	* Admission	Present					Desoxycorticosterone Acetate	Added Sodium Chloride gm.	Adrenal Cortex Extract	
Male			Tuberculous	8.0	Pretexisting hypertension	190/130	170/110	42.9	44.5	1.2	0	Abnormal	Normal	Pellets	0	0	C
			Non-tuberculous	1.0	Puerperal sepsis	90/60	125/80	54.8	59.4	0.2	—	—	Myocardial damage	Pellets	8	0	D
Female			Tuberculous	7.0	None	88/50	136/92	43.5	46.1	1.8	++	Normal	Myocardial damage	Pellets	0	0	C
			Non-tuberculous	3.0	None	85/72	120/80	51.3	54.5	2.8	++	—	Myocardial damage	Pellets	10	0	D
Male			Non-tuberculous	4.0	Hypothyroidism	92/60	130/80	61.2	62.7	3.2	++	Normal	Myocardial damage	Pellets	5	0	A
			Non-tuberculous	5.0	None	96/54	100/60	66.0	68.2	2.1	—	Normal	Normal	Pellets	0	0	A
Female			on-tuberculous	4.0	Urticaria	60/40	110/90	49.6	62.7	2.6	++	—	"Borderline"	Pellets	3	0	A
			on-tuberculous	5.0	Hypoproteinemia	94/60	110/70	55.9	54.7	3.3	++	—	Myocardial damage	Pellets	0	0	A
Male			on-tuberculous	2.0	Anemia	90/58	100/84	47.1	42.7	1.0	++	Abnormal	Normal	Pellets	3	0	B
			on-tuberculous	11.0	None	88/70	100/80	58.3	63.6	1.8	+	—	Normal	Pellets	4	0	B
Female			on-tuberculous	4.0	Pregnancy	102/80	110/78	71.8	69.3	2.3	0	Normal	Normal	Pellets	3	0	A
			on-tuberculous	7.0	None	106/76	120/80	72.0	70.0	1.1	++	Abnormal	"Borderline"	Pellets	0	6 c.c.	A
Male			on-tuberculous	5.0	Active tuberculosis	85/60	138/92	39.3	47.7	3.3	++	—	Normal	Pellets	0	0	A
			on-tuberculous	3.0	None	120/75	130/90	70.9	71.1	2.3	0	—	"Borderline"	Pellets	0	0	A
Female			on-tuberculous	2.0	Arthritis, arteriosclerosis	80/62	132/80	50.8	54.7	0.5	—	—	Normal	Pellets	10	0	D
			on-tuberculous	5.0	Peptic ulcer	92/70	160/100	55.2	70.7	2.3	—	—	Myocardial damage	Pellets	0	0	A
Male			on-tuberculous	3.0	None	80/60	150/106	50.2	58.2	1.3	++	Abnormal	Normal	Pellets	3	3 c.c.	B
			on-tuberculous	5.0	Active tuberculosis	104/68	146/104	57.4	59.2	1.8	++	—	Myocardial damage	Pellets	10	0	D
Female			on-tuberculous	1.0	Active tuberculosis	80/50	130/80	52.7	52.3	0.3	—	—	Myocardial damage	Pellets	0	0	C
			on-tuberculous	2.0	Diverticulosis of sigmoid	90/65	115/65	52.7	59.6	2.1	0	—	Myocardial damage	Pellets	0	0	C
Male			on-tuberculous	6.0	Active tuberculosis	124/76	138/82	81.0	83.6	0.1	++	—	Normal	Pellets	0	0	A
			on-tuberculous	5.0	Healed pulmonary tbc.	118/80	140/88	60.0	68.2	2.3	++	Abnormal	"Borderline"	Pellets	6	0	B
Female			on-tuberculous	2.0	Rheumatic heart disease	100/50	108/60	40.7	41.0	0.9	++	Abnormal	Myocardial damage	Pellets	0	0	B
			on-tuberculous	2.0	None	100/60	112/75	41.5	43.1	0.2	++	Abnormal	Myocardial damage	Pellets	4	0	D
Male			on-tuberculous	6.0	None	94/60	118/82	54.4	63.6	3.3	++	Normal	"Borderline"	Pellets	0	0	A
			on-tuberculous	9.0	None	95/60	140/90	51.0	58.1	3.3	++	Abnormal	Myocardial damage	Pellets	0	0	B
Female			on-tuberculous	3.0	Arthritis	120/78	158/90	58.5	66.1	2.8	++	Normal	Myocardial damage	Pellets	5	0	B
			on-tuberculous	4.0	Coronary occlusion	108/70	122/78	71.2	75.5	2.8	++	—	Myocardial damage	Pellets	0	3 c.c.	C
Male			on-tuberculous	3.0	Healed pulmonary tbc.	80/60	140/80	57.3	61.4	1.8	0	—	Myocardial damage	Pellets	7	0	C
			on-tuberculous	3.0	Healed pulmonary tbc.	80/60	140/80	57.3	61.4	1.8	0	—	Myocardial damage	Pellets	5	0	A

rone acetate treatment was instituted or substituted for some other form of therapy.

imbed. Data for "present weight" and "blood pressure" are the values reported shortly before death. Under "present therapy" are requirements during the period of survival on desoxycorticosterone acetate therapy.

roved. C = unimproved. D = dead.

administration of saline and glucose solutions. That the results of therapy are not due primarily to the extract and supplementary sodium chloride therapy is indicated by the mortality rate of 42 per cent which was reported in a group of 34 patients treated with extract and sodium chloride alone (chart 3) and by the fact that at least 60 patients in the present group are receiving only desoxycorticosterone acetate without supplementary sodium chloride or extract therapy.

It is unfortunate that at present commercial adrenal cortex extracts are not assayed for their "carbohydrate-regulating" potency since the benefits to be derived from this factor constitute one of the principal reasons for administering extract to patients in crisis and during the course of intercurrent infections. Furthermore, it has recently been demonstrated³⁸ that certain adrenal steroids which possess "carbohydrate-regulating" potency actually facilitate sodium and chloride excretion in contrast to the well known sodium and chloride-retaining effect of desoxycorticosterone acetate. It appears probable that a combination of these steroid compounds in correct proportions may not only supplement the deficiency of desoxycorticosterone acetate in respect to "carbohydrate-regulating" potency but may also decrease the tendency for excessive sodium and chloride retention which frequently occurs with rather moderate maintenance doses of desoxycorticosterone acetate.

Studies of electrolyte metabolism, plasma volume, carbohydrate metabolism, electrocardiogram, electroencephalogram, renal, hepatic, muscle and gastrointestinal function emphasize the widespread damage which may occur in patients with adrenal insufficiency. Since many of these changes appear to be irreversible, every effort should be made to establish the diagnosis as early as possible in the course of the disease. Diagnosis of Addison's disease at the time of its onset, however, presents an extremely difficult problem. The use of "deprivation" tests, such as the Cutler-Power-Wilder test,³⁹ is justified if the patient can be kept in a hospital under very careful supervision. A test described more recently by Robinson, Power and Kepler⁴⁰ presents several advantages over the Cutler-Power-Wilder test, and it is certainly advisable to consider applying this test before carrying out procedures which entail much greater risk. Glucose tolerance tests, particularly the response to intravenously administered glucose,⁴¹ and a study of the 17-ketosteroid excretion are of considerable aid.⁴¹ When carefully controlled with adequate periods of placebo medication, we have found the response to sodium chloride and hormone therapy (desoxycorticosterone acetate 2 to 5 mg. daily or adrenal cortex extract, 5 to 10 c.c. daily) to be helpful. More specific, however, is the speed and extent of *relapse which follows the sudden withdrawal of therapy after it has been maintained for a period of one to two weeks.*⁴²

SUMMARY

1. One hundred and fifty-eight patients with Addison's disease have been treated with synthetic desoxycorticosterone acetate of whom 148 have re-

ceived subcutaneous implantations of crystalline pellets of synthetic hormone. An analysis of the entire group revealed the following:

- (a) Tuberculosis appeared to be the etiological factor responsible for the adrenal cortical insufficiency in less than 50 per cent of the patients.
- (b) Approximately 80 per cent of the total number of cases occurred in patients 20 to 50 years of age.
- (c) The difference in incidence between sexes was not great, i.e., males 56 per cent.
- (d) Presenting symptoms were as follows: weakness and fatigability in 100 per cent; increasing pigmentation in 94 per cent; anorexia in 91 per cent.

2. Approximately 90 per cent of the patients required 1 to 5 mg. daily of hormone in oil, injected intramuscularly, or 2 to 10 pellets (125 mg. each) implanted subcutaneously. The average duration of therapy was 1.7 years.

3. The mortality rate for the entire group of 156 patients was 15.4 per cent during the present period of therapy (1.7 years); 46 per cent of the deaths were due to infections and 29 per cent to cardiovascular disease. Sixty of these patients are now receiving desoxycorticosterone acetate treatment alone, 66 patients are receiving synthetic hormone and supplementary sodium chloride medication, and six patients are receiving supplementary daily injections of adrenal cortical extract.

4. A detailed analysis of the results of therapy in 64 patients studied in the Johns Hopkins Hospital revealed that 48, or 75 per cent, of the group were definitely improved, and that 56 per cent of the male patients have now been restored to full time employment. In this group of 64 patients an average gain in weight of 4 kg., and a rise in blood pressure from 100 mm. Hg systolic and 66 mm. diastolic to 126 mm. Hg systolic and 70 mm. diastolic were noted. The effect of synthetic hormone on the abnormal pigmentation was neither striking nor consistent.

5. A high proportion of patients with Addison's disease was observed to show:

- (a) abnormalities in carbohydrate metabolism (75 per cent).
- (b) abnormal electrocardiograms (60 per cent).
- (c) abnormal electroencephalograms (69 per cent).
- (d) abnormalities in creatine metabolism (69 per cent).
- (e) reduced hippuric acid excretion (100 per cent).

These abnormalities persisted despite continued desoxycorticosterone acetate, and in certain instances the extent or incidence of the abnormalities increased during the period of therapy.

6. Desoxycorticosterone acetate treatment was followed by transient hypertension (34 per cent), transient edema (27 per cent), circulatory insufficiency (8 per cent), tendon and muscular contractions (4 per cent) and transient peripheral motor paralysis (2 per cent). Practically all

of the over dosage phenomena may be explained on the basis of excessive retention of sodium and chloride. For this reason the dose of supplementary sodium chloride medication, if used at all in conjunction with desoxycorticosterone acetate, must be regulated carefully. A diet of low potassium content is definitely contraindicated in patients under treatment with desoxycorticosterone acetate. The incidence of undesirable complications may be reduced greatly by care in the regulation of the dose of synthetic hormone and by an appreciation of the mechanism by which complications are initiated.

CONCLUSION

The use of desoxycorticosterone acetate in the treatment of a large group of patients with Addison's disease has been associated with the rehabilitation of approximately 50 per cent of the patients. A striking reduction in mortality rate was observed at the end of 1.5 years of therapy. The disturbances in function which may persist despite desoxycorticosterone acetate therapy have been indicated and the undesirable effects of excessive doses of synthetic hormone have been described. If reasonable care is employed in regulating the dose of hormone, complications resulting from overdosage may be greatly reduced. The functional changes which develop in the heart, brain, liver, kidney, muscle, gastrointestinal tract and skin of patients with long-standing adrenal cortical deficiency demonstrate the protean nature of the disease and indicate the great need for early diagnosis.

Acknowledgments

This report would not have been possible without the continued coöperation of a large group of physicians who were kind enough to provide us with information relating to the hormone assay, implantation of pellets and subsequent clinical course of patients under their care. We also wish to acknowledge the assistance of Miss Rachel Fee, nurse in charge of the metabolism unit, Miss Janet Ruth Engebretson, dietitian-in-charge, and Drs. Marshall Clinton, Jr., and John Arthur Luetscher, Jr. We are indebted to Dr. Warfield M. Firor, Associate Professor of Surgery, for implanting pellets in the patients who were studied in the Johns Hopkins Hospital.

BIBLIOGRAPHY

1. THORN, G. W., HOWARD R. P., EMERSON, KENDALL, JR., and FIROR, W. M.: Treatment of Addison's disease with pellets of crystalline adrenal cortical hormone (synthetic desoxycorticosterone acetate) implanted subcutaneously, *Bull. Johns Hopkins Hosp.*, 1939, lxiv, 339.
2. THORN, G. W., HOWARD, R. P., and EMERSON, KENDALL, JR.: Treatment of Addison's disease with desoxycorticosterone acetate, a synthetic adrenal cortical hormone (preliminary report), *Jr. Clin. Invest.*, 1939, xviii, 449.
3. CLAGGORN, R. A., FOWLER, J. L. A., and WENZEL, J. S.: The treatment of Addison's disease by synthetic adrenal cortical hormone (desoxycorticosterone acetate), *Canad. Med. Assoc. Jr.*, 1939, xli, 226.
4. FERNANDEZ, J. W., RAGAN, CHARLES, ATCHLEY, D. W., and LOEB, R. F.: Desoxycorticosterone esters: certain effects in the treatment of Addison's disease, *Jr. Am. Med. Assoc.*, 1939, cxlii, 1725.
5. THORN, G. W., and FIROR, W. M.: Desoxycorticosterone acetate therapy in Addison's disease. Clinical consideration, *Jr. Am. Med. Assoc.*, 1940, cxiv, 2517.

6. CONYDEARE, J. J., and MILLIS, G. C.: Observations on 29 cases of Addison's disease treated in Guy's Hospital between 1904 and 1923, *Guy's Hosp. Rep.*, 1924, lxxiv, 369.
7. ROWNTREE, L. G., and SNELL, A. M.: A clinical study of Addison's disease, *Mayo Clin. Monographs*, 1931, W. B. Saunders Co., Philadelphia.
8. RICHTER, C. P.: Sodium chloride and dextrose appetite of untreated and treated adrenalectomized rats, *Endocrinology*, 1941, xxix, 115.
9. ANDERSON, E., HAYMAKER, W., and HENDERSON, E.: Successful sublingual therapy in Addison's disease, *Jr. Am. Med. Assoc.*, 1940, cxv, 2167.
10. THORN, G. W., GREIF, R. L., COUTINHO, S. O., and EISENBERG, H.: Relative effectiveness of several methods of administering desoxycorticosterone acetate, *Jr. Clin. Endocrinol.*, 1941, i, 967.
11. THORN, G. W., KOEFF, G. F., LEWIS, R. A., and OLSEN, E. F.: Carbohydrate metabolism in Addison's disease, *Jr. Clin. Invest.*, 1940, xix, 813.
12. LEWIS, R. A., KUHLMANN, D., DELBUE, C., KOEFF, G. F., and THORN, G. W.: The effect of the adrenal cortex on carbohydrate metabolism, *Endocrinology*, 1940, xxvii, 971.
13. THORN, G. W., and LEWIS, R. A.: Acute hemolytic streptococcus infections complicating Addison's disease. Treatment with sulfadiazine and adrenal cortex extract: report of 2 cases, *Jr. Am. Med. Assoc.*, 1942, cxviii, 214.
14. BUELL, M. V., and TURNER, E.: Cation distribution in the muscles of adrenalectomized rats, *Am. Jr. Physiol.*, 1941, cxxxiv, 2.
15. KUHLMANN, D., RAGAN, C., FERREBEE, J. W., ATCHLEY, D. W., and LOEB, R. F.: Toxic effects of desoxycorticosterone esters in dogs, *Science*, 1939, xc, 496.
16. DUQUE SAMPAYO, A., LOPEZ MORALES, J. M., and LAFUENTE, A.: Studien über Physiopathologie der Nebennieren. Der Zustand des Herzens bei der chronischen Nebenniereninsuffizienz (Addison'sche Krankheit), *Endocrinologie*, 1934, xiv, 22.
17. MATTIOLI, M.: L'elettrocardiogramma nella sindrome di Addison, *Cuore e Circol.*, 1937, xxi, 406.
18. McCULLAGH, E. P., and RYAN, E. J.: Use of desoxycorticosterone acetate in Addison's disease, *Jr. Am. Med. Assoc.*, 1940, cxiv, 2530.
19. McGAVACK, T. H.: Changes in heart volume in Addison's disease and their significance, *Am. Heart Jr.*, 1941, xxi, 1.
20. WILLSON, D. M., RYNEARSON, E. H., and DRY, T. J.: Cardiac failure following treatment of Addison's disease with desoxycorticosterone acetate, *Proc. Staff Meet. Mayo Clin.*, 1941, xvi, 168.
21. ASHMAN, R. and HULL, E.: *Essentials of electrocardiography*, 2nd Edition, 1941, Mac-Millan Co., New York.
22. CHAMBERLAIN, E. N., and HAY, J. D.: Normal electrocardiogram, *Brit. Heart Jr.*, 1939, i, 105.
23. LARSEN, K., and SKULASON, T.: Study of 2400 electrocardiograms of apparently healthy males, *Am. Heart Jr.*, 1941, xxii, 625.
24. WHITE, P. D., CHAMBERLAIN, F. L., and GRAYBIEL, A.: Inversion of the T-waves in Lead II caused by a variation in position of the heart, *Brit. Heart Jr.*, 1941, iii, 233.
25. NICHOLSON, W. M., and SOFFER, L. J.: Cardiac arrhythmia in experimental suprarenal insufficiency in dogs, *Bull. Johns Hopkins Hosp.*, 1935, lvi, 236.
26. STEWART, H. J., SMITH, J. J., and MILHORAT, A. T.: Electrocardiographic and serum potassium changes in familial periodic paralysis, *Am. Jr. Med. Sci.*, 1940, cxcix, 789.
27. HOFFMANN, W. C., LEWIS, R. A., and THORN, G. W.: The electroencephalogram in Addison's disease, *Bull. Johns Hopkins Hosp.*, 1942, lxx, 335.
28. THORN, G. W.: Creatine studies in thyroid disorders, *Endocrinology*, 1936, xx, 628.
29. THORN, G. W.: Unpublished data.
30. THORN, G. W., and TIERNEY, N. J.: Myasthenia gravis complicated by thyrotoxicosis: creatine studies, *Bull. Johns Hopkins Hosp.*, 1941, lxix, 469.

31. TALBOTT, J. H., PECORA, L. J., MELVILLE, R. S., and CONSOLAZIO, W. V.: Renal function in patients with Addison's disease and in patients with adrenal insufficiency secondary to pituitary pan-hypopituitarism, *Jr. Clin. Invest.*, 1942, xxi, 107.
32. PERLA, D., and MARMORSTON, J.: *Natural resistance and clinical medicine*, 1940, Little, Brown & Co., Boston.
33. THORN, G. W., and HARROP, G. A.: The "sodium-retaining effect" of the sex hormones, *Science*, 1937, lxxxvi, 40.
34. ROGGOFF, J. M., and STEWART, G. N.: Studies on adrenal insufficiency; influence of "heat" on survival period of dogs after adrenalectomy, *Am. Jr. Physiol.*, 1928, lxxxvi, 20.
35. SWINGLE, W. W., PARKINS, W. M., TAYLOR, A. R., HAYS, H. W., and MORRELL, J. A.: Effect of estrus (pseudo pregnancy) and certain pituitary hormones on life span of adrenalectomized animals, *Am. Jr. Physiol.*, 1937, cxix, 675.
36. GAUNT, R., and HAYS, H. W.: Life-maintaining effect of crystalline progesterone in adrenalectomized ferrets, *Science*, 1938, lxxxviii, 576.
37. SHEEHAN, H. L.: Simmond's disease due to post partum necrosis of anterior pituitary, *Quart. Jr. Med.*, 1939, viii, 277.
38. THORN, G. W., ENGEL, L. L., and LEWIS, R. A.: The effect of 17-hydroxycorticosterone and related adrenal cortical steroids on sodium and chloride excretion, *Science*, 1941, xciv, 348.
39. CUTLER, H. H., POWER, M. H., and WILDER, R. M.: Concentration of chloride, sodium and potassium in urine and blood, *Jr. Am. Med. Assoc.*, 1938, cxi, 117.
40. ROBINSON, F. J., POWER, M. H., and KEPLER, E. J.: Two new procedures to assist in the recognition and exclusion of Addison's disease: a preliminary report, *Proc. Staff Meet. Mayo Clin.*, 1941, xvi, 577.
41. FRASER, R. W., FORBES, A. P., ALBRIGHT, F., SULKOWITCH, H., and REIFENSTEIN, E. C., JR.: Colorimetric assay of 17-ketosteroids in urine, *Jr. Clin. Endocrinol.*, 1941, i, 234.
42. THORN, G. W.: Adrenal insufficiency and the use of synthetic adrenal cortical hormone, *Proc. Inter-State Postgraduate Medical Assembly of North America*, Oct. 14-18, 1940.

PRIMARY SPLENIC NEUTROPENIA; A NEWLY RECOGNIZED SYNDROME, CLOSELY RELATED TO CONGENITAL HEMOLYTIC ICTERUS AND ESSENTIAL THROMBOCYTOPENIC PURPURA *

By B. K. WISEMAN, F.A.C.P., and CHARLES A. DOAN, F.A.C.P.,
Columbus, Ohio

THE spleen may no longer be regarded as an organ of complete mystery. Out of ancient and modern superstitious musings and the obscurity of an incomplete, controversial and largely hypothetical pathologic hematology have gradually emerged sufficient facts relating to splenic structure and functions to compare favorably with current knowledge of the other abdominal viscera. The pioneer work of Barcroft, McNee, Lord Dawson, and Krumbhaar, in creating sound fundamental concepts of physiologic splenic functions has been supplemented by thorough controlled studies of human pathologic splenic diseases, with improved technics by the clinical hematologists, Kaznelson, Frank, Dameshek, Doan and Wiseman among others. Not only practical advances in the treatment of well established splenic syndromes but also recognition of previously unsuspected entities have inevitably followed. The present communication reports what is believed to be a hitherto unrecognized cause of neutropenia, resulting from a pathologically altered, physiologic function of the normal spleen.

Anatomically, the spleen may be regarded as consisting of three structures: (1) the reticulo-endothelial system, (2) the lymphatic component and (3) the vascular spaces. Each of these plays a definite rôle in the physiology of the mammalian organism as a whole. There are, of course, in common with other tissue structures, still some obvious gaps in our knowledge, but none the less, some of the more important of these physiologic activities of the spleen are now well established. Chart 1 presents a diagrammatic summarization of the generally accepted functions together with current concepts corresponding to the abnormalities characteristic of and related to certain clinical diseases.

The essential phagocytic activity of the cells of the reticuloendothelial system for red and white blood cells, platelets, bacteria and other foreign particulate matter has long been known and may be readily observed in any laboratory in which the study of fresh tissues supravitaly stained is undertaken. Any intensification of this physiologic phagocytosis of other cells *may produce* a pathologic disequilibrium characterized by a sharp diminution in one or more of the circulating elements in the blood. Whether the splenic phagocytes increase in number and destructive activity through abnormal hereditary or environmental stimuli, or whether they respond secondarily to fundamental alterations in the blood elements themselves, which

* Received for publication January 16, 1942.

THE FUNCTIONS OF THE SPLEEN

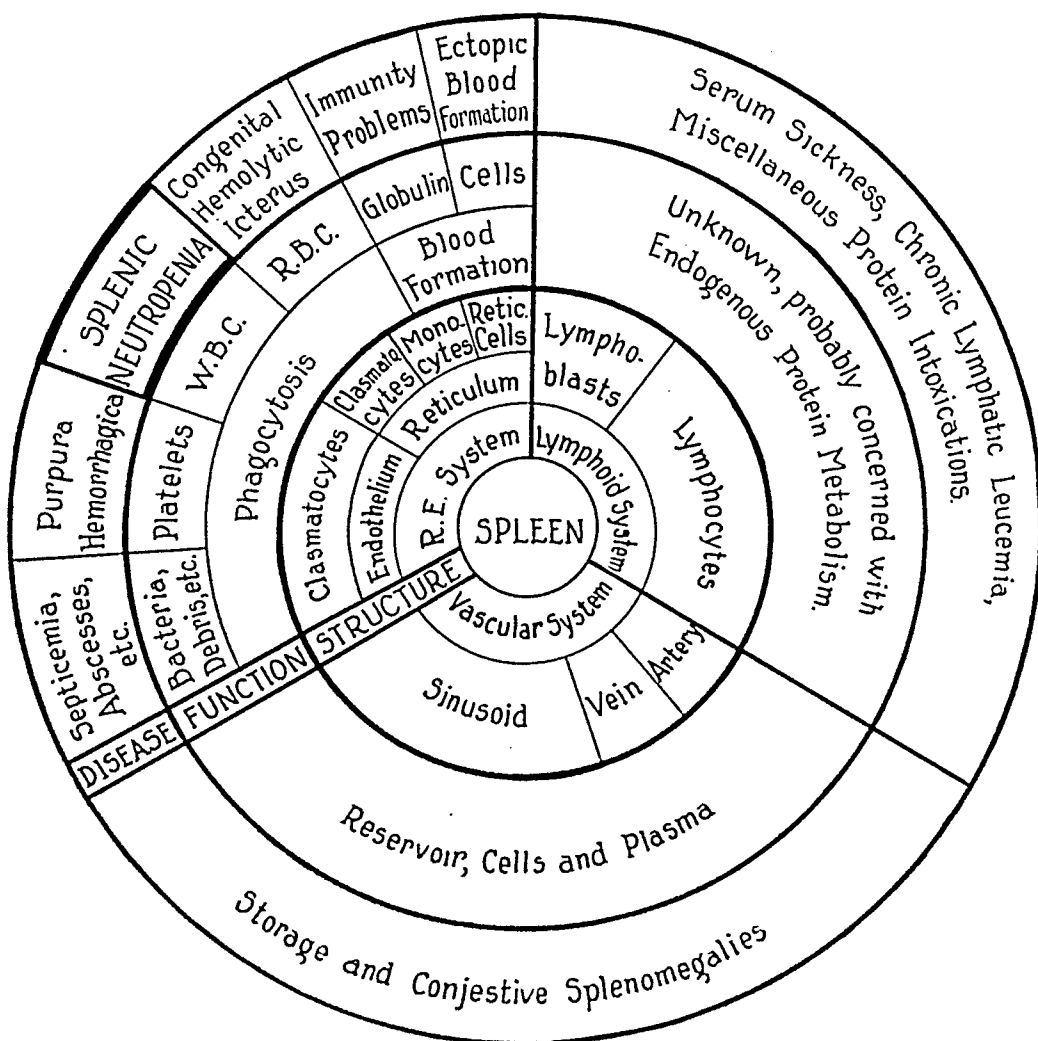


CHART 1. The functions of the spleen. This diagram is drawn to show the relationships between structural elements of the spleen and their physiologic functions. Added to this in the outermost circle are shown certain pathologic states that may result from alteration of these physiologic functions. The inner circle is represented by the structural components of the spleen. Arranged in radial fashion from each of these units is placed the corresponding function of each element. For example, the reticulo-endothelial component of the spleen consists of endothelium and reticulum cells; from the former are derived clasmatocytes, and from the latter clasmatocytes, monocytes and daughter reticulum cells. The clasmatocytes (chiefly) but also the monocytes dispose of effete cellular elements and foreign substances by phagocytosis (next to outer circle). A disturbance (pathologic increase) in this function when directed principally against the neutrophilic leukocytes may result in severe neutropenia (the splenic neutropenia of the outermost circle); when the accelerated phagocytosis is directed against other elements, the other diseases shown may result.

questration in essential thrombocytopenic purpura, both of which may be corrected completely by successful splenectomy.

On theoretical grounds alone, and by analogy, a similar overactivity of the splenic macrophages for granulocytes was predicted, and the first cases reported from this clinic at Atlantic City in May 1939.¹ This syndrome

has since been recognized, confirmed, and reported from two other clinics.^{2, 3} The following discussion is the first detailed account of the extended and prolonged observations of the original patients with this granulocytopenic syndrome, after sufficient time may be presumed to have elapsed for any further hematologic or other organic diseases to make their appearance if they were going to develop. Because of the unique nature of this disturbance and certain inevitable and characteristic variations from patient to patient, each case will be presented in some detail.

CASE REPORTS

Case 1. J. M. S.,* female, aged 38; final diagnosis: *acute* splenic neutropenia. This patient had been in normal health until October 4, 1938, ten days before admission to the University Hospital. The first symptoms were interpreted as a mild coryza, self treatment for which consisted of amphetamine by inhalation, nose drops (Vicks) and one aspirin tablet. Eight days later her throat became sore and she was seen by her family physician for the first time. A blood count was taken and a marked leukopenia (1900 per cu. mm.) with only 14 per cent neutrophils was found. She was seen in consultation on the same day by one of us (B. K. W.) who made the following observations in the home: temperature 102, pulse 98, respirations 20. The throat was diffusely red and there was an ulcerated area on the mucosa of the right posterior pharynx about one half cm. in diameter. There was a slight generalized lymphadenopathy and the spleen was felt at the left costal border during quiet respirations, descending approximately two cm. upon deep inspiration. A purpuric area of spontaneous origin was found on the right lateral aspect of the thigh. The peripheral blood showed 1,400 white cells per cu. mm. with only 10 per cent neutrophils, monocytes and lymphocytes being about equally represented. No pathologic qualitative changes in the white blood cells were seen. Sternal bone marrow aspiration in the home showed no foreign cell infiltration or toxic hypoplasia, but unexpectedly revealed a marked *hyperplasia* of myeloid cells without appreciable "shift to the left," the majority being mature polymorphonuclears and myelocytes "C." The diagnosis was not immediately evident, and suspecting a type of blood dyscrasia not previously observed in this clinic, hospitalization was advised for further study.

Upon admission to the hospital the next day, October 14, additional historical facts were elicited as follows: The patient was of American parentage and had always been in average good health. There had been "growing pains" in childhood without actual swollen or painful joints. Ten years prior to the present admission, however, there had been a chronic recurring mild sinusitis accompanied by painful swelling of most of the larger, as well as some of the smaller joints, but not the spine. The involvement had been migratory in character, but whether these symptoms reflected acute rheumatic fever or rheumatoid arthritis could not be determined. During the eight months preceding the present illness, these symptoms had been entirely absent. A tonsillectomy had been performed in 1926, and there was a miscarriage with curettage in 1932. There was a full term pregnancy with spontaneous delivery of a normal infant six months before the beginning of the present illness. A blood count done in the hospital at that time was reported as normal. The best weight of the patient had been 154 lbs., average weight 138 and present weight 144. A detailed inquiry into the possible ingestion of drugs revealed no additional facts. There was no individual or family history of allergic manifestations. Other routine historical data were not pertinent to the present illness.

*This patient was referred by Dr. H. K. Mouser, of Marion, Ohio, whose cordial cooperation made possible the subsequent studies of this first case identified as splenic neutropenia.

The physical examination of the patient in the hospital revealed no new signs. The temperature was 102.8°, pulse 118, respirations 22, blood pressure, systolic 110, diastolic 80. The laboratory examinations other than the blood (see chart 2) were

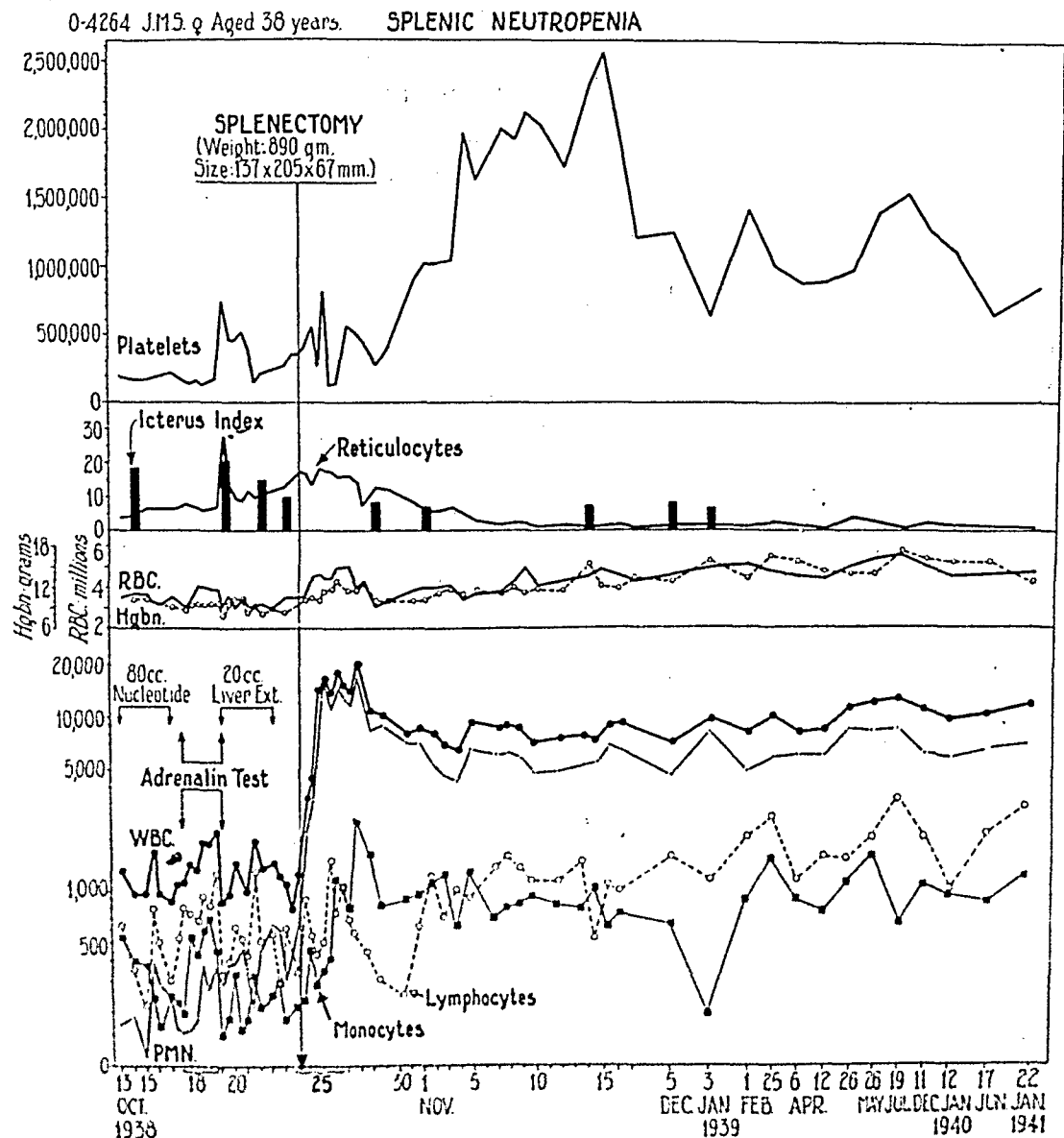


CHART 2. The hematologic data in case 1 before and after splenectomy. The charting of the white blood cells is upon a semi-logarithmic scale. The marked neutropenia, mild thrombocytopenia, and anemia with slight icterus and reticulocytosis are shown to be completely and permanently corrected by the splenectomy of October 25, 1938. The immediate rise in neutrophils on the day of operation is especially noteworthy and characteristic.

of negative rather than positive diagnostic significance. Five urinalyses gave normal chemical and microscopic findings; Wassermann and Kahn reactions were negative; agglutination tests for typhoid, paratyphoid and undulant fever were negative; repeated blood cultures yielded no growth; all blood chemical determinations were normal; liver function test (hippuric acid) was within normal limits; stereoscopic roentgen-ray films of the chest showed mild bronchiectasis at the left base; roentgen-rays of teeth revealed no root abscesses; roentgen-ray films of the sinuses were clear and cultures yielded no pathogenic organisms. A second sternal puncture reaffirmed the essential integrity of the bone marrow for myeloid elements as recorded in table 1.

TABLE I.
Supplement to Chart 2

	Detail of Blood Examinations				Details of Sternal Bone Marrow Examinations	
	Oct. 14, 1938	Oct. 25, 1938		Dec. 5, 1938	Jan. 22, 1941	Oct. 17, 1938
	Admission to Hospital	4 h. before Splenectomy	8 h. after Splenectomy	1 mo. 5 days after Splenectomy	2 yrs. 2 mos. after Splenectomy	8 days before Splenectomy
Total W.B.C.	1,000	1,400	20,000	8,150	11,200	Myeloid Elements
Total R.B.C.	3,710,000	3,650,000	5,030,000	4,680,000	4,870,000	PMN Mature 31
Total Platelets	178,000	350,000	140,800	1,263,000	876,000	Metamyelocytes 12½
Hemoglobin (Gm.)	10.4	10.3	13.0	13.0	13.5	Myelocyte "C" 32
Reticulocytes (%)	4.6	17.6	16.0	1.4	0.8	Myelocyte "B" 14½
Cell Volume R.B.C. (%)	30	30		47	47 *	Myelocyte "A" 2
Sedimentation Index (R.B.C.) (mm./min.)	1.2	1.4		0.8	0.1 *	Myeloblasts 1
Icterus Index	18.6	10		8.0	4 *	PME Myelocyte C 1
Van den Bergh						Lymphocytes 3
Differential Count (%)						Reticulum Cells ½
PMN—Mature	12	52	77	65	61	Plasma Cells ½
Metamyelocytes	4	2	6	0	0	Monocytes 2
Myelocyte "C"	4	2	4	0	0	R.B.C. (No. per 100 W.B.C.)
Myelocyte "B"	0	0	3	0	0	Normoblasts 27
Eosinophiles	0	2	0	4	1	Late
Lymphocytes	36	26	4	22	27	Erythroblasts 6
Monocytes	40	16	6	9	11	Early Erythroblasts 2
Normoblasts	0	1	0	0	0	W.B.C. : R.B.C. Ratio 5 : 1
No. per 100 W.B.C.						
Fragility R.B.C.	.412-.300	.412-.300				Remarks:

Megakaryocytes normal. Marrow shows no pathologic elements. Grossly and microscopically shows hyperplasia.

* Date January 12, 1940.

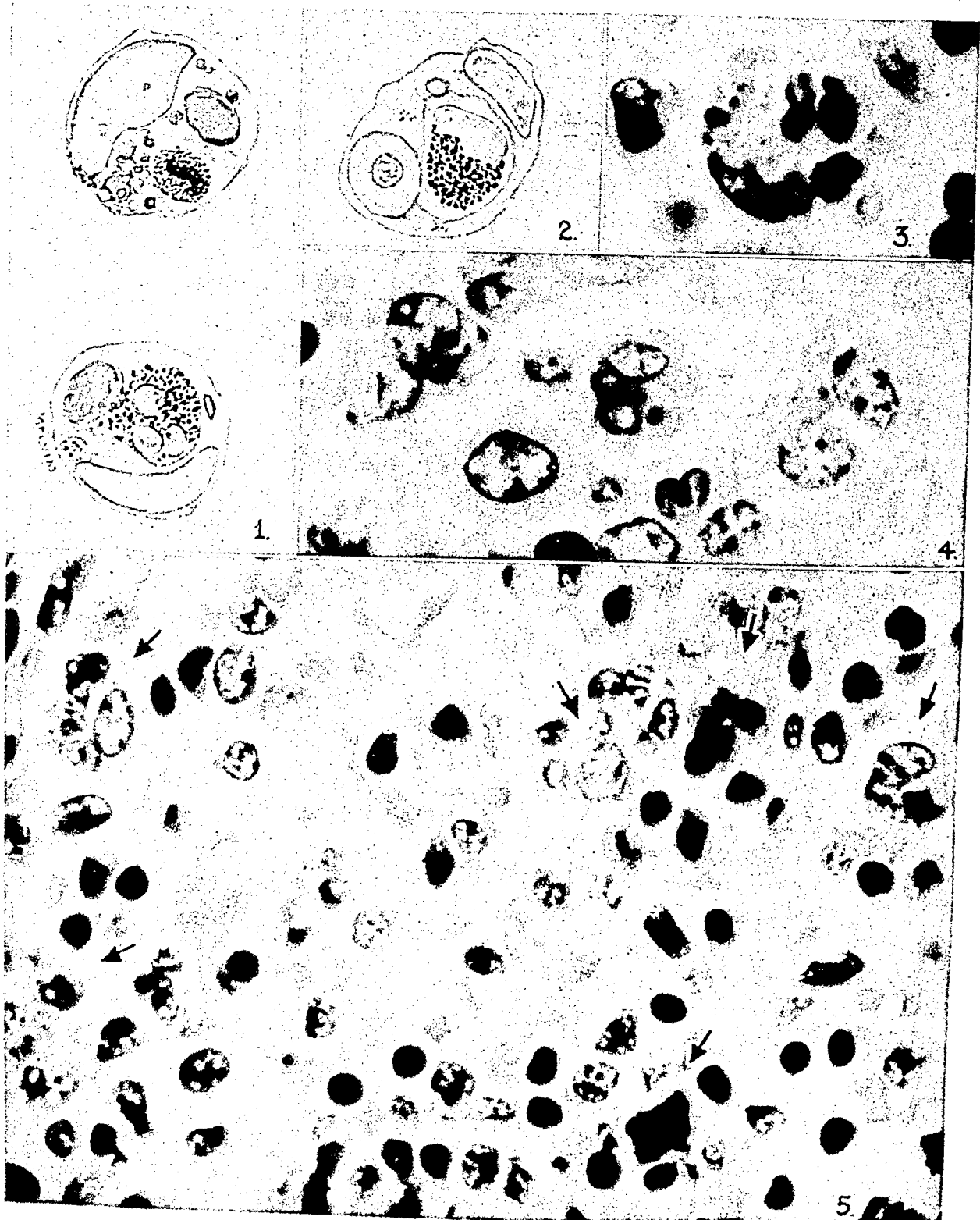


PLATE 1. *Fig. 1.* A drawing of two highly phagocytic clasmotocytes as viewed in supravitality stained scrapings of the pulp from the spleen through the oil immersion lens of the microscope. The material was obtained from case 3. The uppermost cell shows the phagocytosis of a single whole red blood cell, numerous fragmented particles of red blood cells, and a stab type of neutrophile. The lower clasmotocyte contains a three lobed neutrophile, a whole red blood cell and just above the left pole of the nucleus of the phagocyte a mass of platelet cytoplasm that has not yet completely disintegrated.

Fig. 2. A drawing of a clasmotocyte from the same source as figure 1 showing phagocytosis of a myelocyte "C" and a normoblast.

Attempts to treat the persistent leukopenia medically with parenteral administration of pentnucleotides (0.7 gm. every six hours for eight doses), and liver extract (100 units every 12 hours for four doses) were without any demonstrable influence on the white blood cell count or the clinical picture. An adrenalin test showed a small increase of neutrophils from 200 to 350 per cu. mm. which was not deemed significant.

Inasmuch as the patient continued to show a steadily progressive, non-remitting clinical course, with rising temperature (103.5°), enlarging spleen (now 5 cm. below the left costal border during quiet respiration), increasing angina and profound granulopenic leukopenia, further delay was considered unsafe, and splenectomy was advised and accomplished on October 25, 1938 by Dr. George Curtis. An immediate rise in leukocytes occurred post-splenectomy, and after seven hours the peripheral blood showed 20,100 white blood cells, of which 90 per cent were mature, motile neutrophilic granulocytes (see table 1). The subsequent readjustment of the white cells, the over compensatory peak in platelets, and the reestablishment of reticulocytes, red blood cells and icterus at normal levels are shown on chart 2. The patient made a good clinical recovery with only one complication, cystitis of the colon bacillus type, occurring on the tenth day post-operative, which cleared up promptly under mandelic acid treatment. She was discharged on the twenty-first post-operative day. As indicated on the chart, she has been seen frequently since; but no return of the granulopenia has occurred, nor have evidences of leukemia or any other disease appeared to date (June 1942).

At operation, the liver appeared normal, and no evidence of portal hypertension was apparent. The removed spleen weighed 890 gm. and from it 241 gm. of blood could be expressed. The entire peritoneal surface was smooth and there were no adhesions. The elongated organ was a dull muscular red. There was no thickening of the capsule. Scrapings of the pulp substance stained supravitaly showed a marked increase in the phagocytic clasmatoocytes, often 10 or more to an oil immersion field, within which ingested neutrophilic leukocytes predominated with also some mature red blood cells and an occasional normoblast. No other abnormalities of the spleen were determined either supravitaly or upon study of the fixed sections. Plate 1, figures 3 and 5 are photomicrographs of the phagocytic phenomena observed.

Case 2.* B. K., male, aged 50; final diagnosis, *subacute* splenic neutropenia. This patient was admitted to the University Hospital for the first time on September 21, 1938 with the presenting complaint of progressive fatigue. His present illness began two months previously, when his family physician in another city promptly referred him to a hospital for diagnosis. After some 17 days of observation and investigative studies no conclusion was reached, and the patient was discharged after receiving two blood transfusions. He was then admitted to University Hospital where the following studies were directed by one of us (B. K. W.). The patient was a poultry dealer of Jewish extraction who had always been in good health until the

* Referred by Drs. B. S. Kline and S. F. Rosen, Cleveland, Ohio, whose coöperation we gratefully acknowledge.

Fig. 3. Photograph of a highly phagocytic clasmatoocyte from the spleen of case 1. Oil immersion lens and hematoxylin-eosin stained paraffin section. Magnification to correspond approximately with drawings of figures 1 and 2.

Fig. 4. A photograph through the oil immersion lens of a phagocytic clasmatoocyte from the spleen of case 2. Hematoxylin-eosin stained paraffin section. Magnification approximately upon the scale of the drawings shown as figures 1 and 2.

Fig. 5. A photograph of an oil immersion field ($\times 1250$) selected from a paraffin section of the spleen of case 1. At least six highly phagocytic clasmatoocytes (indicated by the arrows) were present in this single field, illustrating the marked increase in number and activity of these cells. The illustration is typical of the density of concentration of the macrophages found in the spleen of this case. Hematoxylin-eosin stain.

advent of symptoms of exhaustion as noted. He had never been exposed to coal tar products, lead or other industrial hazards. He had taken no drugs except aspirin in small quantity. There was no history of allergy or blood diseases in either the patient or his family. Interrogation by systems revealed no relevant data. Physical examination showed as the only significant positive finding an enlarged spleen, extending 6 cm. below the costal border in the mid-clavicular line. The laboratory studies gave the following data: Blood showed marked leukopenia, moderate anemia and thrombocytopenia, and the bone marrow showed myeloid hyperplasia (see table 2); Wassermann and Kahn reactions were negative; urinalysis was negative; hippuric acid and bromsulphalein tests for liver function were within physiologic limits; all blood chemical determinations were normal; basal metabolic rate was $+9$ per cent; stool examinations were negative for occult blood, ova and parasites; gastric analysis showed 1° of free acid in the fasting sample rising steadily to 72° in a specimen 60 minutes after histamine; fluoroscopy of the stomach and colon, and a chest roentgen-ray plate revealed no organic pathologic lesions referable to these areas. The patient remained in the hospital for three days during which the temperature, pulse and respirations were normal. The adrenalin test was positive for excessive splenic sequestration (chart 3). Congenital hemolytic jaundice, hypoplastic anemia and Banti's syndrome were ruled out, but no positive diagnosis could be decided upon, and he was discharged with the request to return for further observations.

Seven weeks later the same patient was re-admitted to the University Hospital. The interval history recorded a steadily increasing weakness and an enlarging tumor mass in the abdomen. Upon physical examination the patient was now found to be clinically jaundiced and the spleen extended 8 cm. below the left costal border. The

TABLE II
Supplement to Chart 3.

	Details of Blood Examinations					
	Sept. 21, 1938	Nov. 8, 1938	Nov. 18, 1938		Dec. 19, 1938	Oct. 27, 1939
	1st Adm. to Hosp.	2nd Adm. to Hosp.	$\frac{1}{2}$ Hour before Splen- ectomy	8 Hours after Splen- ectomy	1 Month, 1 Day after Splen- ectomy	11 Months, 3 Weeks after Splen- ectomy
Total W.B.C.	1,850	1,200	1,000	12,600	4,100	8,500
Total R.B.C.	3,320,000	2,480,000	2,650,000	3,460,000	4,120,000	5,110,000
Total Platelets	185,920	69,440	29,440	560,000	799,280	1,522,780
Hemoglobin (Gm)	10.6	7.5	7.6	10.0	13.0	13.9
Reticulocytes (%)	14.2	12.0	28.0	22.6	0.6	2.2
Cell Volume R.B.C. (%)	32	27	—	—	41	48.5
Sedimentation Index mm./min. R.B.C.	1.7	0.6	—	—	1.4	1.0
Icterus Index	7	20	—	—	7	7
Differential Count						
PMN—Mature	26	24	12	85	34	50
Metamyelocytes	0	2	6	0	0	0
Myelocyte "C"	0	2	0	0	0	0
Myelocyte "B"	0	0	0	0	0	0
Eosinophiles	16	6	2	0	10	1
Basophiles	6	0	0	0	3	0
Lymphocytes	40	44	62	1	36	35
Monocytes	12	22	18	14	17	14
Normoblasts						
No. per 100 W.B.C.	0	0	0	0	0	0
Frangibility R.B.C.	471-519	430-500	—	—	430-500	380-282

TABLE II (Continued)

	Details of Sternal Bone Marrow Examination			
	Sept. 21, 1938	Nov. 8, 1938	Dec. 14, 1938	April 5, 1939
	1st Admission to Hospital	2nd Admission to Hospital	26 days—Post Splenectomy	4 Mos. 17 days—Post Splenectomy
Myeloid Elements				
PMN Mature	38	19	39.5	58
Myelocytes "C"	36.5	56	28.5	24
Myelocytes "B"	4.0	8	3.0	2
Myelocytes "A"	0	0	1.0	0
Myeloblasts	0	0	0.5	0
B.M.B.	0.5	0	1.0	0
PME Mature	3.5	3.5	2.0	2
PME Myelocytes "C"	6	0	1.0	2.5
PME Myelocytes "B"	0.5	0	0	1.0
Lymphocytes	4.5	4.5	11.0	6.0
R.E. Cells	0.5	1.0	0	0
Plasma Cells	3.0	3.0	2	2
Monocytes	0.5	3.0	9	1.5
Clasmatocytes	0.5	1.0	1	1.0
RBC (No. per 100 WBC)				
Normoblasts	119	98	46	35
Late Erythroblasts	99	8	2	5
Early Erythroblasts	18	5	3	1
Megakaryocytes	1	0	0.5	0
WBC : RBC Ratio	1 : 2.36	1 : 1.1	2 : 1.1	3 : 1.2
Remarks:	No. Path. Cells seen.			

neutropenia, the hemolytic anemia and thrombocytopenia had become more severe (see table 2 and chart 3) and the bone marrow more hyperplastic, so that it seemed clear that the enlarged spleen was the responsible agent. A diagnosis of splenic neutropenia was made and splenectomy was successfully accomplished on November 18, 1938, by Dr. G. M. Curtis with hematologic and clinical results entirely comparable with those already noted in case 1. (See chart 3.) The liver appeared normal at operation, and there were no evidences of portal hypertension. The spleen closely resembled grossly and microscopically that of case 1. No abnormality could be determined except the excessive phagocytosis of neutrophilic leukocytes and erythrocytes, which was most strikingly seen in the supravital stained scrapings of the splenic pulp, as illustrated on plate 1, figure 4. The patient developed severe abdominal pain in the left upper mid-abdomen on the third post-operative day, which persisted for 10 days and was thought to be due to splenic vein thrombosis although the exact nature of this temporary abdominal distress was never proved. The patient was discharged to his home on December 19, 1938, with all blood elements essentially normal (table 2). Repeated follow-up observations have shown no return of the original or of any other blood dyscrasia, and this man has continued in normally good health throughout the past 3½ years.

*Case 3.** L. B., female, aged 67; final diagnosis: *chronic splenic neutropenia*. This patient was admitted for the first time to the University Hospital on October 21, 1937, with the chief complaint of progressive weakness during the past four months. She was subjected to a diagnostic study by one of us (C. A. D.) and the following facts were obtained: The history revealed that the patient had been in usual health

* Referred by Dr. Mark D. Godfrey, Columbus, Ohio, whose coöperation we gratefully acknowledge.

until the spring of 1937 when she noted some slight diminution in energy. The degree of exhaustion gradually increased until by September she was forced to spend the greater portion of her time in bed. She was given iron for anemia by her local physician, but became nauseated and discontinued it. Seen later by another physician, the leukopenia was found and 10 doses of pentnucleotide of 10 c.c. each were given with no improvement. No other drugs were taken. She had had a mild but persistent,

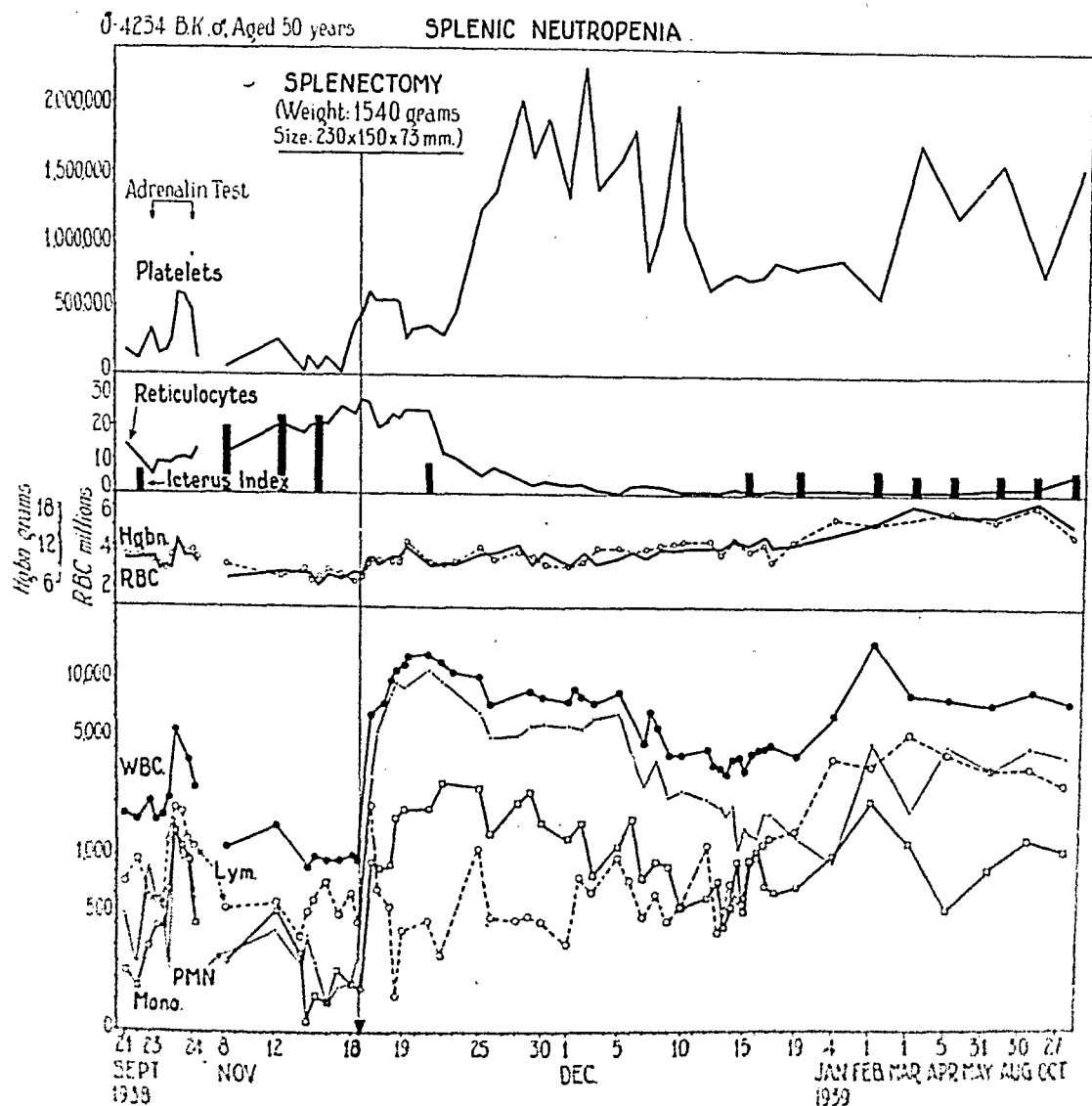


CHART 3. The hematologic findings in case 2 before and after splenectomy. The white cells are charted upon a semi-logarithmic scale. The break in the lines from September 24, 1938, to November 8, 1938, represents a period in which the patient was out of the hospital and blood studies were not obtained. The immediacy of the results after the removal of the spleen is clearly shown. Corrections in levels of red cells, icterus, reticulocytes, and platelets are also apparent. This patient really exhibited a hypersplenism directed toward all the circulating blood elements but chiefly toward the granulocytes.

chronic, non-productive cough "all her life." For the previous seven years there had been from time to time some tenderness and swelling of various joints, chiefly the fingers, but these symptoms had been absent for two months prior to admission. No other relevant data were elicited. The physical examination showed nothing unusual for a person of this age except an enlarged hard spleen extending 8 cm. below the costal border. The leukopenia (650) was the most profound we had ever encountered,

with the sternal marrow hyperplastic (see table 3, and chart 4). Urinalysis was within normal limits; phenolsulphonphthalein kidney function test was within normal limits. Liver function tests: bromsulphalein excretion was normal, and hippuric acid test showed excretion of 2.36 grams in two hours. All blood chemical determinations were normal; glucose tolerance test showed mild diabetic type of curve; electrocardiogram revealed marked myocardial damage; chest roentgen-ray plate showed diffuse fibrosis with an oval area on the right side that was interpreted as a thickening of the pleura, probably the result of an old healed empyema; fluoroscopy of the stomach and colon showed no organic pathology. A Banti's syndrome was suspected and splenectomy was advised, but refused by patient and family because of age and the apparently great surgical risk. Before discharge the patient was given 12 c.c. of liver extract over a period of 10 days without any improvement.

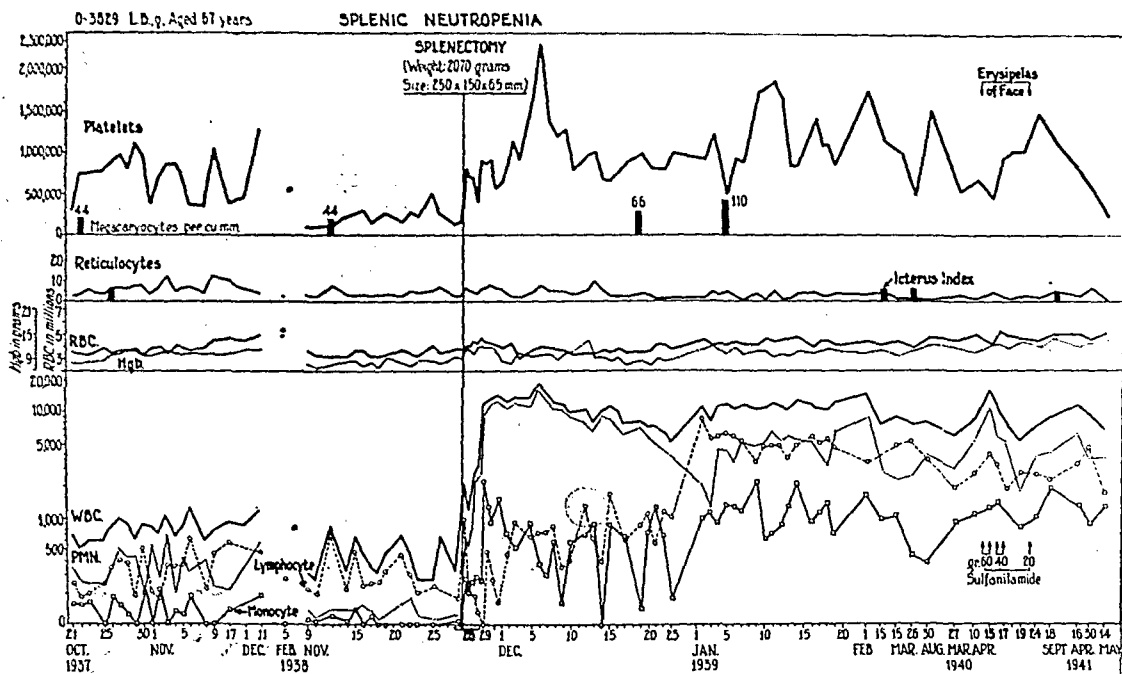


CHART 4. The hematologic data, case 3, before and after splenectomy. The period from December 1, 1937, to November 9, 1938, represents the interval between the first and second admissions to the hospital. The granular cells were almost completely absent from the peripheral blood prior to splenectomy during the second hospital admission. Sixteen months following splenectomy during which time permanent correction of the neutropenia was observed, the patient suffered an attack of facial erysipelas. The customary neutrophilic leukocytosis incident to this disease is well shown on this chart, prompt recovery following sulfanilamide therapy. Only the white cells are charted upon a semi-logarithmic scale.

Approximately one year later, November 9, 1938, this patient was again brought to the clinic and re-admitted to the Research Service. During the interim she had become increasingly weaker, more dyspneic, and had developed a purulent conjunctivitis. An ulceration had appeared two months earlier on the right lower leg from an abrasion of the skin, which gradually spread, failing to respond to any treatment. When examined in the hospital, the ulcer crater measured $5\frac{1}{2}$ cm. in diameter by $\frac{1}{2}$ cm. deep. The spleen of this patient had continued to enlarge until it was found to extend deep into the left pelvis inferiorly. No lymphadenopathy was apparent. The blood examination showed a still more profound leukopenia (150), there being only 25 to 30 neutrophilic leukocytes per cu. mm. of blood. There was also a more definite

thrombocytopenia with red cells, hemoglobin and reticulocytes relatively unchanged. There was no jaundice. An examination of the sternal bone marrow showed a maintained hyperplasia of the myeloid elements, mostly at the myelocyte "C" level (see table 3). The lowest circulating granulocyte level occurred on November 18 at which time only 1 per cent neutrophils were found in a total white cell count of 300 per cu. mm. The highest value was recorded on November 16, 25 per cent neutrophils in a total count of 450 white blood cells. Other pertinent laboratory studies were as follows: Liver function tests showed 2.63 gm. hippuric acid excreted, galactose tolerance test showed no galactose excreted, no bromsulphalein dye (5 mg. per kilo) was found in circulation at end of 30 minutes. The total serum proteins were 6.1 per cent; serum calcium 10.2 mg. per cent. The basal metabolism was +26 per cent. The phenolsulphonphthalein kidney function test showed a dye excretion of 60 per cent in two hours, with urinalysis normal. The temperature during the 19 days in the hospital before splenectomy varied between 97.8° and 101.4° F. Symptomatic therapy was of no benefit, and at this time both patient and family asked for splenectomy.

Splenectomy was accomplished on November 28, 1938, by Dr. G. M. Curtis. There was no free fluid in the abdominal cavity nor any evidence of venous engorgement. The liver was normal in size and appearance. The spleen was freely movable with no adhesions and, when removed, weighed 2,070 gm. In addition, a large accessory spleen, measuring 2 by 2 by 1½ cm., was extirpated. Supravital stained scrapings of the pulp of the spleen showed a marked increase in phagocytic clasmatocytes or macrophages, most of which were actively destroying neutrophilic leukocytes (see plate 1, figures 1 and 2). Exactly 35 minutes after the splenic pedicle had been

TABLE III
Supplement to Chart 4

	Details of Blood Examination					
	Oct. 21, 1937	Nov. 9, 1938	Nov. 28, 1938		Jan. 2, 1939	May 14, 1941
	1st Admission to Hospital	2nd Admission to Hospital	½ h. before Splen- ectomy	8 h. after Splen- ectomy	1 mo. 3 days after Splen- ectomy	2 yrs. 5½ mos. after Splen- ectomy
Total W.B.C.	650 3,690,000 310,000 8.5 2.8 30 0.9 6.6 48 2 0 0 2 0 32 16 0 412-300	150 3,600,000 79,200 8.0 3.0 — — — 20 5 0 0 0 0 70 5 0 —	300 3,790,000 151,600 9.4 2.8 — — — 15 5 0 0 0 0 70 10 0 —	3,300 4,600,000 892,000 11.8 5.2 36 1.0 — 81 6 0 0 0 0 2 8 0 —	11,450 4,570,000 914,000 11.1 1.4 38 0.6 — 18 0 0 0 0 73 9 0 —	6,300 4,810,000 230,000 13.9 0.4 — — — 54 0 0 0 0 26 20 0 —

TABLE III (Continued)

	Details of Sternal Bone Marrow Examination		
	Oct. 21, 1937 1st Admission to Hospital	Nov. 15, 1938 2nd Admission to Hospital	Jan. 5, 1939 1 mo. 7 days after Splenectomy
Myeloid Elements			
PMN Mature	2.5	0	2.0
Myelocytes "C"	59.0	92.5	80.0
Myelocytes "B"	20.5	1.0	4.5
Myelocytes "A"	2.5	0	0.5
Myeloblasts	0	0	0
P.M.B.	1.5	1	0.5
P.M.E. Mature	1.5	2.0	0
P.M.E. Myelocytes "C"	4.5	2.0	2.5
P.M.E. Myelocytes "B"	0.5	0	0
Lymphocytes	5.0	0	5.5
R. E. Cells	0	0	0
Monocytes	0.5	0	0.5
Plasma Cells	2.0	0.5	1.0
Clasmatocytes	0	0	0.5
R.B.C. (No. per 100 W.B.C.)			
Normoblasts	17	23	64
Late Erythroblasts	5.5	21	19
Early Erythroblasts	2.5	17	1
Megakaryocytes	0	1.0	2.5
W.B.C. : R.B.C. Ratio	4 : 1	2 : 1.2	2 : 1.6

clamped the white blood count was 2,250 with 32 per cent neutrophils; six hours post-splenectomy the white blood cells were 3,350 with 84 per cent of the cells neutrophilic leukocytes; 24 hours later the white blood count was 11,850 with 78 per cent neutrophils. The post-operative course was uneventful, without any complications, and it was interesting to note that the chronic ulceration of the right leg healed even before the abdominal incision. In April 1940, this patient, now 70 years of age, suddenly developed an acute fulminant erysipelas of the face, and was admitted to the University Hospital on the third day of her illness with a high fever and semi-comatose. Sulfanilamide was given in the dosage indicated on chart 3 with immediate improvement and prompt recovery. The leukocytic reaction was a characteristic and adequate response to infection, completely substantiating the fundamental integrity of the bone marrow in this patient. She has continued well to the present time (January 1942).

Case 4. T. V., female, aged 12; final diagnosis: *subacute* splenic neutropenia and thrombocytopenia (chart 5). This girl was admitted to the Research Service, University Hospital, May 6, 1941, where the studies were directed by one of us (C.A.D.). The chief complaints were anorexia, weakness, persistent low grade fever, frequent epistaxes, bleeding gums, and generalized ecchymoses and petechiae of skin and mucous membranes. The patient had been in usual health until February 5, 1941, when she became ill with what was diagnosed as "influenza and bronchitis with sore throat and enlarged cervical lymph glands." One week after the initial onset, small subcutaneous ecchymoses appeared first on the arms and subsequently in "crops" over the entire body, which phenomenon continued up to and including the time of admission. Some 20 epistaxes were reported, the last having continued for 24 hours just prior to entering the hospital. A "diarrhea" of four to five "tarry" stools daily had persisted for two weeks, with a weight loss only from 74 to 71 lbs. The patient is said by the mother never to have been physically strong or rugged, having suffered more or less severely from all childhood diseases, and having always "bruised easily."

Family history was non-contributory for blood dyscrasias. The significant physical findings on admission were: temperature 100° F., pulse 88, respirations 24, blood pressure systolic 114, diastolic 60; pallor of skin and mucous membranes with numerous petechial hemorrhages scattered over chest, abdomen, back and extremities, and large

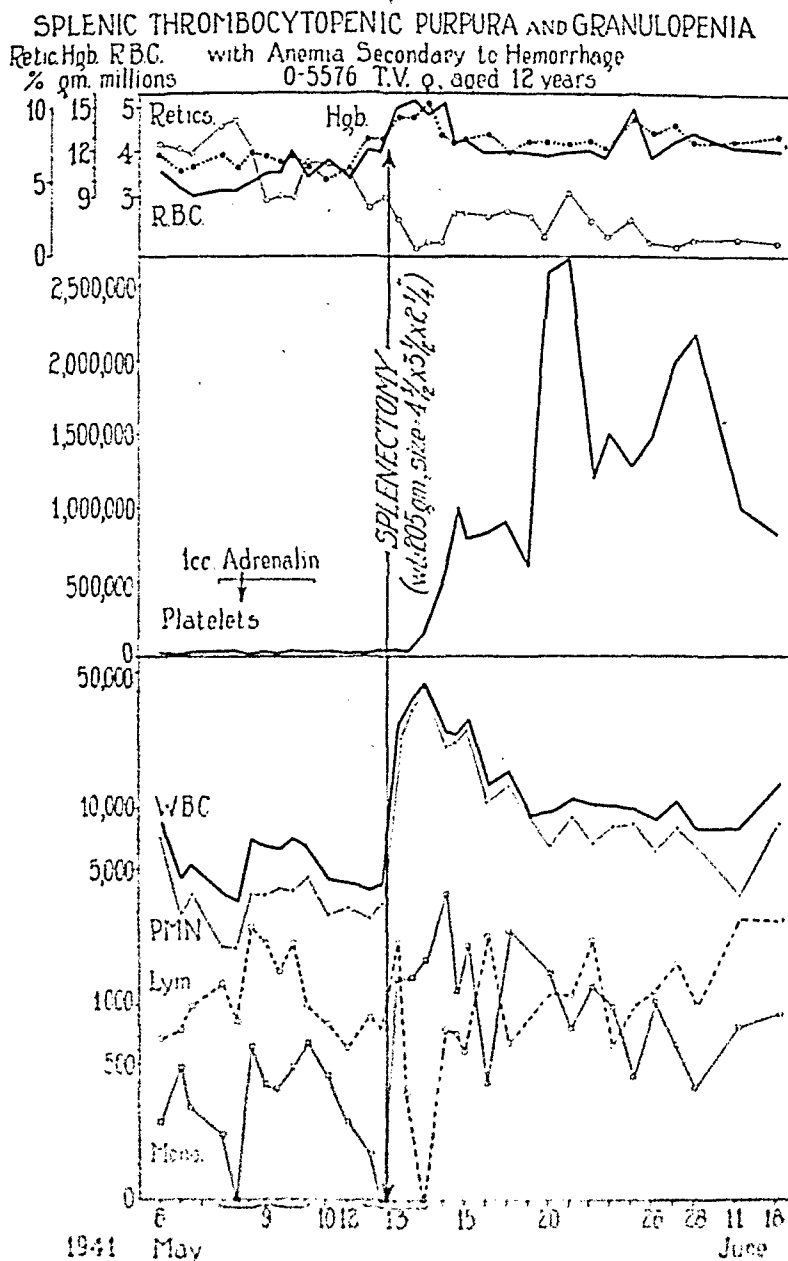


CHART 5. The hematologic data in case 4 before and after splenectomy. This case illustrates a type of hypersplenism in which the chief effect is exerted upon the platelets, whereas the neutrophilic leukocytes are depressed only moderately. The correction of levels of platelets and granulocytes was prompt and permanent. Note particularly the temporarily extremely high levels of both of these elements shortly following splenectomy. The charting of the white blood cells is upon a semi-logarithmic scale.

data: total white blood cells 3400 to 5100, despite recent hemorrhages; total red blood cells 3,000,000 to 3,250,000; hematocrit 33 per cent; hemoglobin 11 gm. per 100 c.c.; reticulocytes 6.8 to 9.2 per cent; *blood platelets 6400 to 32,000 per cu. mm.* (normal 700,000); corrected erythrocyte sedimentation rate 0.3 mm. per minute (normal); erythrocyte fragility range .412 to .300; icterus index 5; prothrombin 60 per cent; representative supravital differential count of the white blood cells showed polymorphonuclear neutrophils 56 per cent, eosinophils 4 per cent, lymphocytes 34 per cent, monocytes 6 per cent, without significant qualitative abnormalities; bleeding time was 6½ minutes, Howell's coagulation time 10 minutes with delayed clot retraction. Hippuric acid excreted was 3.7 gm., urinalysis was essentially physiologic; serological tests for syphilis were negative. The sternal bone marrow on May 8 was grossly hyperplastic with red rather than gray tissue flecks; microscopically by actual count the RBC:WBC ratio was 5.1; normoblasts predominated with frequent mitotic figures observed in the few erythroblasts and occasional megaloblasts present; the myeloid elements were largely neutrophilic and at the myelocyte C or relatively mature stage with a few eosinophils; the megakaryocytes appeared to be increased both relatively and in absolute number, as many as three being found in one oil immersion field, and were seen in every stage of immaturity from young, large mononuclear megakaryocytoblasts through intermediate to large, typical, mature granular megakaryocytes; only one plasma cell, an extremely rare phagocytic macrophage, and no monocytes or other cells foreign to normal bone marrow were encountered. The interpretation was, generalized pan-marrow hyperplasia of all normal cell types, with a significant left shift only in megakaryocytes, without evidence of toxic destruction or maturational arrest, therefore, a reflection of excessive peripheral demands for all types of circulating elements. The adrenalin test on May 9 showed a maximum rise in total white blood cells from the base line of 3450 to 7100 at the end of 15 and 50 minutes; red blood cells rose from 3,250,000 to 4,100,000 at the end of 50 minutes, and hemoglobin 11 gm. to 12 gm.; the platelets fluctuated between 32,500 and 14,000, the lower figures being recorded during the test.

Both the granulopenic leukopenia and splenomegaly, proved by direct and indirect evidence, are incompatible with a simple diagnosis of essential thrombocytopenic purpura. In no other instance of uncomplicated splenic purpura in our experience to date has the spleen been clinically palpable or at operation been found to be enlarged. The evidence seemed to justify the pre-operative diagnosis of thrombocytopenic purpura and granulocytopenic leukopenia, both attributable to splenic hypersequestration with compensatory marrow hyperplasia which also included the red cells a reaction secondary to the purpuric hemorrhages. Following parenteral administration of vitamin K and a blood transfusion of 200 c.c. to secure hemostasis, splenectomy was successfully accomplished on May 13 by Dr. Curtis. The temperature rose no higher post-operatively than the pre-operative base line between 100 and 101° F., and became normal for the first time in four months on the fifth post-operative day. On the day of operation the total white cell count rose from 3900 with 74 per cent polymorphonuclear neutrophils at 9:00 a.m. to 44,400 with 96 per cent polymorphonuclear neutrophils by 3:45 p.m., the spleen having been removed about 11:00 a.m. The red blood cells increased from 4,090,000 to 5,200,000, and the blood platelets from 16,400 to 165,580. This astounding increase in circulating granulocytes immediately following operation, in the absence of any infection or complication, reflects the tremendous compensatory hyperplasia of myelocytes in the bone marrow and the less stable hemolytopoietic equilibrium which we always find in children. The increase of approximately one million red blood cells per cu. mm. represents the reservoir sequestration of these elements in the enlarged spleen. The following day the platelets were 509,000 per cu. mm. and by the seventh post-operative day had risen to 2,616,000 per cu. mm. under the released productive capacity of the megakaryocytes. Under adrenalin

stimulation after exposure, the spleen contracted to approximately one-third of its gross size as first observed before the pedicle was clamped, and when removed, measured $4\frac{1}{2}$ by $3\frac{1}{2}$ by $2\frac{1}{4}$ inches and weighed 205 grams. Immediate supravital studies of the splenic parenchyma revealed a most striking abnormal segregation of polymorphonuclear neutrophils, an occasional myelocyte C and eosinophilic granulocyte, and from one to three very large, highly phagocytic macrophages per oil immersion field containing many myeloid elements, fewer red blood cells, and much smaller material which could be interpreted as platelet debris. There was the usual number of qualitatively normal lymphocytes, and no increased fibrosis and no other pathologic cells or tissue changes were apparent. The patient was discharged on the fourteenth post-operative day in normal hematopoietic and clinical equilibrium, and when last seen June 18, 1941 she had 13,600 white blood cells, 4,270,000 red blood cells, hematocrit of 41 per cent, 13 gm. of hemoglobin, 832,000 blood platelets, 65 per cent polymorphonuclear neutrophils, 7 per cent eosinophils, 21 per cent lymphocytes, and 7 per cent monocytes.

Case 5. C. G., male, aged 34 years; final diagnosis: *subacute* splenic neutropenia, with thrombocytopenia and hemolytic anemia. This patient was well until May 5, 1938 when he developed a cough, sore throat, fever, and complained of easy exhaustion. A diagnosis of influenza was made by his physician. He did not improve, and the first record of a blood examination was made one month later at which time he was said to have an anemia. He was placed on liver and iron therapy but without improvement. A sternal marrow aspiration done at this time was reported as normal. Within the space of two months he received 11 blood transfusions. On December 19, 1938 an enlarged spleen was discovered and deep roentgen-ray therapy was given. During the succeeding nine weeks of his hospitalization he received two additional transfusions and two therapeutic injections of typhoid vaccine. In the meantime there had been four bone marrow studies, the last one of which was interpreted as "aplastic." Liver and iron were continued without improvement. Bleeding of the gums developed about one month prior to admission to the University Hospital. The past history included symptomatic and radiological evidence of peptic ulcer of 12 years' duration. The patient was a glazier by occupation but had had no contact with lead.

Upon admission to the University Hospital research service (B. K. W.) the physical examination showed a well nourished but apprehensive male patient of the stated age with an icteric pallor to the skin, sclerae, and mucous membranes. Minimal but generalized adenopathy was present with an enlarged spleen extending two cm. below the left costal border. No other significant physical abnormalities were noted. The laboratory data included: peripheral neutropenic leukopenia, moderate anemia and marked thrombocytopenia (chart 6). The bone marrow differentials revealed pan-hyperplasia for all elements but more particularly the nucleated red cells. Urinalysis was normal. The basal metabolic rate was minus 21 per cent; checked at minus 22 per cent. The Wassermann and Kahn reactions were negative. The hippuric acid excretion was 4.5 gm. in two hours. The blood chemistry revealed a fasting blood sugar of 112 mg. per cent, blood urea nitrogen of 15 mg. per cent, total proteins of 7.5 per cent. The electrocardiogram showed a slight left axis deviation, and the chest roentgen-ray was negative for any pathologic process. The temperature and pulse were within physiologic limits. Splenectomy was performed on May 12, 1939 by Dr. V. A. Dodd, of the Department of Surgery. The presence of a duodenal ulcer was confirmed, but all other abdominal viscera appeared normal except

cated that seen in congenital hemolytic icterus following splenectomy.⁵ The post-operative convalescence was complicated by temporary atelectasis of the left lung, followed by a mild bronchopneumonia, non-specific in type, which resolved satisfactorily, the patient being discharged on June 14, 1939. When seen two months after operation, the patient had no symptomatic complaints, and all the cellular elements were normal qualitatively and quantitatively in both blood and bone marrow. This recovery has been maintained up to and including the present writing (2½ years).

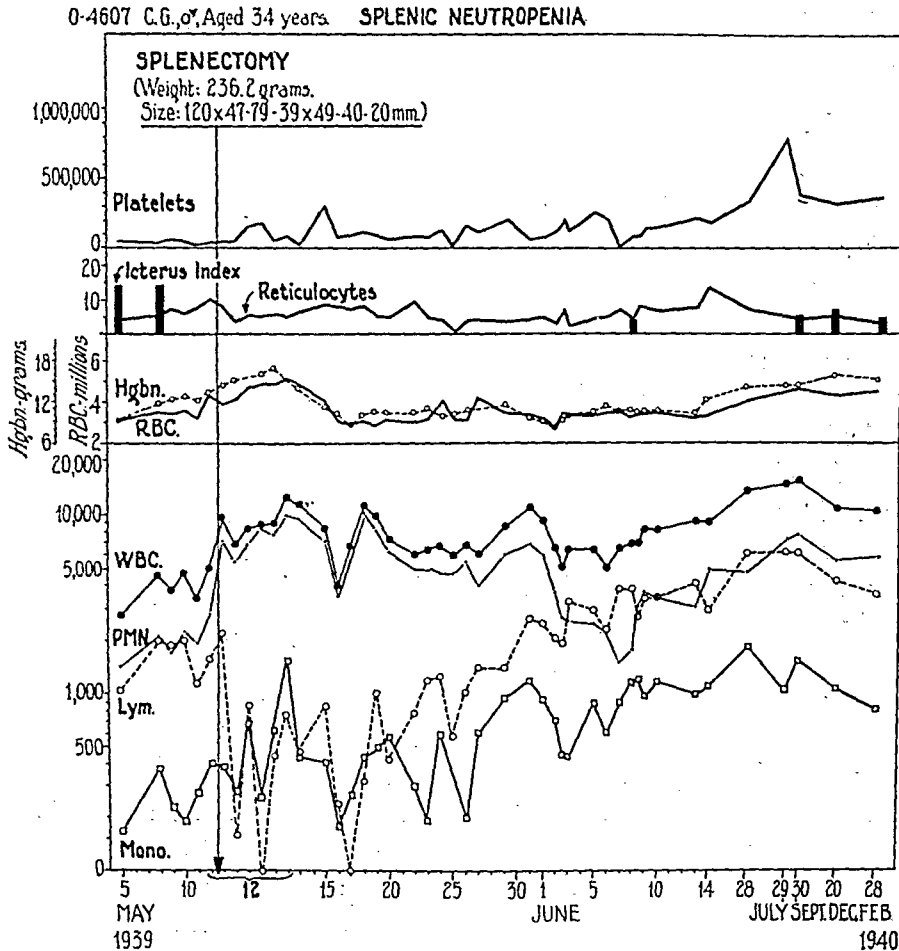


CHART 6. The hematologic findings in case 5 before and after splenectomy. Prior to operation this patient presented a depression chiefly of the platelets and granulocytes. The increase of the platelets to normal levels following splenectomy was relatively slow, that of the neutrophilic leukocytes was immediate. The charting of the white blood cells is upon a semi-logarithmic scale.

DISCUSSION

An analysis of the preceding cases shows the "common denominator" of all to have been profound granulopenia, panhyperplasia of the marrow and splenomegaly, with splenectomy curative. Varying degrees and combinations of hemolytic anemia and thrombocytopenic purpura were encountered and coincidentally corrected. In each case the anemia was hemolytic in type, with elevated reticulocyte count and icterus with negative direct van den

Bergh reaction. Case 1 showed principally neutropenia but also definite thrombocytopenia and hemolytic anemia. Case 2 although exhibiting chiefly neutropenia when first seen, had developed two months later not only a more profound neutropenia, but also a hemolytic anemia and thrombocytopenia of rather severe grade. Case 3 showed the most extreme and pure example of neutropenic leukopenia, at no time evidencing any hemolytic anemia, but developing some non-symptomatic thrombocytopenia by the second admission. Case 4 is instructive from the standpoint of the thrombocytopenic purpura which was the most striking presenting feature upon hospitalization, but probably represented a secondary manifestation of primary splenomegalic neutropenia when all of the facts are weighed critically. Case 5 showed initial infection with subsequent neutropenia and icteric anemia, and finally bleeding gums (thrombocytopenia), all of which disappeared after splenectomy. From these facts there is little doubt that a single mechanism is responsible for the various degrees of anemia, neutropenia or thrombocytopenia in this group of cases, especially when it has been demonstrated that all three elements are increased following splenectomy. In addition, it has been shown through direct supravital studies of the splenic parenchyma that there is a marked increase in number and phagocytic activity of the macrophages, each one of which is seen to be actively destroying not only neutrophilic leukocytes (and in some instances myelocytes) but also red blood cells, including normoblasts to a lesser degree. One can only conclude that the syndrome is directly a result of hypersplenism, in which there is not only an accentuation of the physiologic function of disposing of effete, senile or damaged circulating blood elements, but also the development of a pathologic predilection for young, nucleated, as well as normal mature cells. We visualize this syndrome, therefore, as closely akin to congenital hemolytic icterus and essential thrombocytopenic purpura and possessing a comparable mechanism. In the former disease, the activation of the clasmatoocytes of the spleen is directed chiefly toward the red blood cells, in the latter chiefly toward the thrombocytes, and in the neutropenic syndrome chiefly toward the neutrophilic leukocytes. A review of our cases of congenital hemolytic icterus and thrombocytopenic purpura reveals that each is often accompanied by a more or less definite reduction in other circulating units, including the white cells.

It is not felt that the syndrome discussed in this paper is to be confused with Banti's syndrome since in no instance has there been any functional or direct evidence of portal hypertension or cirrhosis of the liver. Furthermore, Banti's syndrome is always characterized by recurring anemia secondary to esophageal or gastric hemorrhages, never by a hemolytic type of anemia, the latter being quite definite in several of our cases. And in the patients described here, purpura was occasionally observed, but seldom if ever massive hemorrhages, and none of the spleens removed at operation in our syndrome of leukopenia showed the histopathologic features described for Banti's syndrome.

The limited data available in Felty's⁶ reported cases do not permit either of their inclusion or exclusion in the syndrome described. Two of our patients had a history of joint pains, but this symptom was negligible during the acute neutropenic episodes. Felty's original five cases each showed a moderate leukopenia but in no instance so severe a neutropenia as in our series. Although a slight secondary anemia was recorded, jaundice was not mentioned nor other evidence given upon which to postulate an underlying hemolytic mechanism. Hanrahan's case⁷ of Felty's syndrome, except for the arthritis which was a prominent feature, more closely parallels the present series in that there was an appreciable anemia and thrombocytopenia, and it is stated that "larger cells exhibiting red blood cell phagocytosis were plentiful in the sinuses" of the spleen. Restitution of both red and white blood cells to normal was found months after splenectomy. As has many times been pointed out and as our own experience has verified, atrophic arthritis is often associated with some anemia and a moderate leukopenia, and in the young individual there is often splenomegaly (Still's disease). As Felty himself pointed out, his syndrome may represent Banti's disease with coincidental arthritis, although he believed he was dealing with a different clinical entity. Williams⁸ in reporting a case of so-called Felty's syndrome, suggests that it may represent a primary disturbance of blood formation in which there is an arrest of maturation of the granulocytes. Postmortem studies showed a diminution in granulopoiesis in the bone marrow, the direct opposite of the findings in all of our cases. Cravens' case⁹ resembles our syndrome only remotely. Price and Schoenfeld's case¹⁰ with postmortem studies showed only a very slight neutropenia. There was a minor degree of myeloid hyperplasia in the bone marrow but no change in the spleen such as we have described. Without sufficient data in each individual case precisely to define its limits and, therefore, its mechanism of production, these overlapping syndromes must remain symptomatically closely related but probably etiologically distinct. The therapeutic approach to each clinical problem must depend upon the accurate determination of its fundamental, underlying cause.

Furthermore, we do not believe that we are describing a syndrome that is fundamentally an infectious process, although, like congenital hemolytic icterus and probably essential thrombocytopenic purpura, the clinical and hematologic features may become apparent or the syndrome be precipitated during or following an infection. The association of splenomegaly and leukopenia with a wide variety of chronic infections is too well known to require extended comment; however, the combination of thrombocytopenia, severe neutropenia with myeloid hyperplasia in the bone marrow and hemolytic anemia are not the classical features of chronic infections.

Malignant neutropenia, drug induced or otherwise, is readily differentiated by a good history, clinically by absence of an enlarged spleen and hematologically by the bone marrow which is hypoplastic for myeloid elements with marked maturation arrest.¹¹

Leukemia of sub-leukemic myeloid type may present the most difficult differential diagnosis. Here a critical examination of bone marrow supplementing carefully made blood studies is all important in that splenic neutropenia never shows the qualitative alterations in the myeloid elements which characterize the myeloid leukemias.

TABLE IV
Splenic Neutropenia

Diagnosis

I. Clinical:

1. Splenomegaly
2. Occasionally purpura (depends on degree of associated thrombocytopenia)
3. Occasionally oral ulceration (depends on acuteness and severity of neutropenia)
4. Occasionally mild icterus (depends on degree of associated anemia)

II. Hematology

1. Bone marrow
 - a. Hyperplastic for myeloid series and, if hemolytic anemia is pronounced, erythroid series.
 - b. No abnormal cells present
 - c. Not leukemic
2. Blood
 - a. Marked specific neutropenia
 - b. Anemia when present is macrocytic, hyperchromic in type
 - c. Reticulocytosis if anemia is definite
 - d. Increased indirect van den Bergh depending on grade of anemia
 - e. Thrombocytopenia variable

A summary of the essential diagnostic criteria is given in table 4. In general, from a clinical standpoint we feel that the presence of an easily palpable non-tender spleen is the most important feature. If, then, a severe neutropenic leukopenia with variable even though slight anemia and thrombocytopenia is found and if the bone marrow shows panhyperplasia including the myeloid elements without maturation arrest or pathological alterations, the diagnosis should be sufficiently certain to justify the therapeutic test of splenectomy.

We feel that the completeness of the recovery and the time interval that four of these patients have survived since our preliminary report¹ without any signs of relapse definitely eliminates any other diagnosis or mechanism such as hypoplastic anemia or subleukemic leukemia.

CONCLUSIONS

1. A newly recognized syndrome characterized by marked neutropenia and splenomegaly has been described. It is suggested that this be termed essential or primary splenic neutropenia, inasmuch as evidence is adduced to show that the basic mechanism is hypersplenism in which an accelerated destruction of the granular leukocytes of the circulating blood by the reticulo-endothelial cells of the spleen takes place.

2. The disease is apparently permanently cured by removal of all splenic tissue, and the patients are restored to normal hemolytopoietic equilibrium.

3. Although this syndrome may superficially resemble Banti's syndrome, Felty's syndrome, sub-leukemic myeloid leukemia, hypoplastic anemia, ma-

ligniant neutropenia, or certain types of chronic infection in one or more particulars, it nevertheless is a separate and distinct entity based solely upon splenic dysfunction. In this respect primary splenic neutropenia is more closely related to congenital hemolytic icterus and essential thrombocytopenic purpura, each of these predominant clinical and hematologic syndromes blending into and involving to a greater or lesser degree the other. The reticulo-endothelial cells of the spleen when on a rampage of destruction, may selectively choose as victim any *one* of the elements of marrow origin passing through this organ, but more often than not other "innocent bystanding" elements suffer likewise in some degree. Splenectomy always is followed by an increase in *all* circulating blood elements whenever applied in any one of these conditions.

4. An accurate final diagnosis may be achieved only after complete clinical information plus detailed studies of both the blood and bone marrow.

BIBLIOGRAPHY

1. WISEMAN, B. K., and DOAN, C. A.: A newly recognized granulopenic syndrome caused by excessive splenic leucolysis and successfully treated by splenectomy, *Jr. Clin. Invest.*, 1939, xviii, 473.
2. MOORE, C. V., and BIERBAUM, O. S.: Chronic neutropenia treated by splenectomy, *Internat. Clin.*, 1939, iii, 86-95.
3. MUETHER, R. O., MOORE, L. T., STEWART, I. W., and BROWN, G. O.: Chronic granulocytopenia caused by excessive splenic lysis of granulocytes, *Jr. Am. Med. Assoc.*, 1941, cxvi, 2255-2257.
4. WISEMAN, B. K., DOAN, C. A., and WILSON, S. J.: Present status of thrombocytopenic purpura, with special reference to diagnosis and treatment, *Jr. Am. Med. Assoc.*, 1940, cxv, 8-13.
5. DOAN, C. A., CURTIS, G. M., and WISEMAN, B. K.: Hemolytopoietic equilibrium and emergency splenectomy, *Jr. Am. Med. Assoc.*, 1935, cv, 1567-1574.
6. FELTY, A. R.: Chronic arthritis in adult, associated with splenomegaly and leucopenia, *Bull. Johns Hopkins Hosp.*, 1924, xxxv, 16-20.
7. HANRAHAN, E. M., and MILLER, S. R.: Effect of splenectomy in Felty's syndrome, *Jr. Am. Med. Assoc.*, 1932, xcix, 1247-1249.
8. WILLIAMS, R. H.: Felty's syndrome; report of case with necropsy findings, *ANN. INT. MED.*, 1936, ix, 1247-1255.
9. CRAVENS, E. B., JR.: Splenectomy in chronic arthritis associated with splenomegaly and leucopenia (Felty's syndrome), *Jr. Am. Med. Assoc.*, 1934, cii, 823-826.
10. PRICE, A. E., and SCHOENFELD, J. B.: Felty's syndrome; report of case with complete postmortem findings, *ANN. INT. MED.*, 1934, vii, 1230-1239.
11. FITZ-HUGH, T., JR., and KRUMBHAAR, E. B.: Myeloid cell hyperplasia of bone marrow in agranulocytic angina, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 104-111.

NON-OPERATIVE RESULTS IN NINETY PATIENTS WITH ABNORMAL CHOLECYSTOGRAMS *

By STAIGE D. BLACKFORD, M.D., F.A.C.P., ROBERT M. BIRD, JR., M.D.,
and S. WARD CASSCELLS, M.D., *University, Virginia*

THE literature contains many reports indicating the effectiveness of medical treatment in gall-bladder disease. However, Walters and Snell¹ believe that in many of these reports there is an element of wishful thinking in the interpretations of the results. They point out that long-term observations of large groups of medically treated patients are rare, and they cite the report of J. M. Blackford, King and Sherwood² as one of the best. In that report, 200 cases diagnosed clinically as cholecystitis were reviewed by follow-up methods after an average period of nine and one-half years. However, the large majority of these cases were studied before cholecystograms came into use, and hence no attempt could be made to correlate the non-operative results with the cholecystographic examinations. It is the purpose of the present study to analyze the non-operative results obtained in a routine group of 90 patients with abnormal cholecystograms.

Selection of Cases. Records of more than 500 abnormal cholecystograms were found in the files of the Department of Roentgenology of the University of Virginia Hospital from 1925 to 1938. Wilson, Lehman and Goodwin³ reported the results of surgery in 252 of these cases which came to operation. One hundred and eighty-five of the remaining cases had records available which were suitable for this study.

Follow-up Method. A printed questionnaire was mailed to each of these 185 patients and, in most instances, to their local physicians. The questions in the form related to the following: (1) Subsequent indigestion; (2) food idiosyncrasies; (3) occurrence of abdominal pain; (4) occurrence of colic; (5) occurrence of jaundice; (6) treatment followed; (7) subsequent operation; (8) ability to lead a normal life; and (9) patient's own estimate of any change in the status of symptoms after the cholecystogram.

Satisfactory replies were received from 90 of the 185 patients (43.7 per cent). The average period of follow-up in these cases was six and one-half years.

INITIAL CLINICAL DATA

General. The average age was 50.3 years. There were 57 females and 23 males. Five were colored.

Symptoms. The symptoms of these 90 patients were graded from their records at the time of the initial cholecystogram as mild, moderate and severe. In the mild group of 25 patients, there were many who had no symptoms

* Received for publication January 14, 1941.

From the Department of Internal Medicine, University of Virginia Hospital.

referable to the gall-bladder and in whom the cholecystogram was performed merely as a part of a general diagnostic survey. The others in this group were those who suffered with mild dyspepsia. There were 26 patients whose symptoms were classified as moderate, meaning that their general health was fair but that they suffered from bothersome indigestion, right upper quadrant pain, nausea or vomiting, either singly or in combination. None of these cases had either colic or jaundice. The severe group was comprised of the 37 patients who complained of severe right upper quadrant pain, colic, jaundice or frequent severe indigestion, singly or in combination. The patients in this group would probably have been diagnosed clinically as having cholecystitis. The records in two remaining cases were inadequate to grade the severity of symptoms.

Cholecystograms. Of the 69 patients without demonstrable stones, 29 had non-functioning gall-bladders at the time of the original roentgen examination, and 40 patients had poor function. Of the 21 cases with stones, six had non-functioning gall-bladders, nine poor function, and six good function.

Reasons for No Operation. In 33 patients, it was felt that the gall-bladder symptoms were too mild to justify surgical interference. A trial on medical treatment before recourse to surgery was thought advisable in nine instances. Operation was recommended to 23 patients but they refused surgery. The operative risk was considered too great in 17 patients. No cause for delay in surgical treatment could be assigned from the records in eight cases.

TREATMENT

Medical. The exact medical treatment advised in 57 cases is known from the records. It seems reasonable to assume that some similar advice was given to a majority of the remaining patients. Although the medical treatments instituted followed no set routine, in general the following points were stressed: (1) a bland diet suited to the individual's caloric needs and dietary idiosyncrasies; (2) fat content of the diet adjusted to the individual's tolerance; (3) antispasmodic drugs when indicated; (4) choleretic drugs occasionally; and (5) sedatives if necessary. Many patients were placed on a simple bland diet with frequent feedings. It is impossible to say how closely the instructions were followed and what other remedies were used. Numerous patients attributed their improvement to various patent medicines which they had begun on their own initiative.

Surgical. Ten of the 90 patients are known to have come to subsequent cholecystectomy. Three of these had non-functioning gall-bladders, five had poor function, and two had stones.

NON-OPERATIVE RESULTS

Deaths. Fifteen of the 90 patients, on whom questionnaires were returned by their families, are dead. Two of these are said to have succumbed

to "gall-bladder attacks"; neither was subjected to surgery because of their advanced years. Two other fatal cases were jaundiced at the time of the cholecystogram. One of these died in the hospital without diagnosis while awaiting laparotomy. The other died on re-admission for alcoholic hallucinations, apparently from acute hepatitis. In 11 of the 15 fatal cases, death was attributed to causes outside the hepatic and biliary tracts.

Method of Grading the Non-Operative Results. The symptomatic results in the 90 patients were graded in a manner similar to that employed by Wilson, Lehman and Goodwin³:

Grade 1: Excellent results. Good general health without recurrence of symptoms; no food idiosyncrasies; patient able to do ordinary work.

Grade 2: Good results. Good general health with only mild digestive disturbances or occasional upper abdominal fullness; few foods not tolerated; no work loss.

Grade 3: Fair results. Fair health with bothersome digestive upsets with or without right upper quadrant pain; work loss.

Grade 4: Poor results. Poor health; colic or frequent abdominal pain. The patient in this group considers himself the same or worse than before roentgen study.

Patients falling into groups one and two have been termed "satisfactory" and those in groups three and four "unsatisfactory." All cases which came to subsequent operation have been grouped under "unsatisfactory" even though three of these 10 were no better following surgery.

After the 90 questionnaires were graded as satisfactory and unsatisfactory, the results were correlated with: (1) severity of the original symptoms; (2) reason for delayed operation; and (3) initial roentgen report.

1. *Non-Operative Results Correlated with Severity of Original Symptoms.* The results were graded as satisfactory in 68 per cent of those whose original symptoms were classed as mild, in 50 per cent of those classed as moderate, and in 35 per cent of those classed as severe.

2. *Non-Operative Results Correlated with Reason for No Operation.*

Reason	No. of Cases	Total Deaths	Symptomatic Results	
			"Satisfactory"	"Unsatisfactory"
Advised but refused.....	23	4	7	16
Preliminary medical treatment advised.....	9	0	2	7
Too few gall-bladder symptoms.....	33	4	23	10
Too poor operative risks.....	17	5	7	10
Unknown.....	8	2	4	4
Totals.....	90	15	43	47

3. *Non-Operative Results Correlated with Initial Roentgen Report.*

Roentgen-Ray Report	No. of Cases	Total Deaths	Subsequent G. B. oper.	Symptomatic Results	
				"Satisfactory"	"Unsatisfactory"
Poor function.....	40	3	5	21	19
Non-function.....	29	10	3	13	16
Stones					
N.F.....	6	2	1	4	2
P.F.....	9	1	0	3	6
G.F.....	6	0	1	2	4
Totals.....	90	15	10	43	47

It will be seen from the above that the symptomatic results were graded as satisfactory in 47.7 per cent of the entire 90 patients with abnormal cholecystograms, in 52.5 per cent of those with poor function, in 44.9 per cent of those with no function, and in 42.8 per cent of those with cholelithiasis.

COMMENT

The pitfalls of this study are apparent. Aside from the fallacies inherent in all questionnaire follow-ups, the total number of cases is too small for any statistical conclusions. Furthermore, in any attempt at analysis, the total would have to be broken down into even smaller groups on account of the variability in symptomatology and cholecystographic data. However, it seems justifiable to present this material in the hope that it may be amplified by other reports of a similar nature.

It should be pointed out that the results presented here are called non-surgical rather than medical results. It was obvious from the replies that relatively few of these patients followed faithfully the medical régime advised. But even in those who adhered strictly to the instructions given, there was no appreciable favorable difference in the results obtained. It is difficult to see how medical treatment of gall-bladder disease can affect its course other than by relief of symptoms which for the most part are not directly attributable to the gall-bladder itself. It is believed that the results here reported represent to a large extent the natural course of the condition rather than specific results of medical treatment. It should be noted that medical treatment was considered the treatment of choice in only 10 per cent of the present group.

From the symptomatic point of view, many of these patients with abnormal cholecystograms did not have sufficient symptoms to warrant a clinical diagnosis of cholecystitis. However, cholecystitis would presumably have been the clinical diagnosis in the 37 patients whose symptoms were classified as severe. It is interesting that symptomatic relief was graded as "satisfactory" in 35 per cent of this group as compared to 37 per cent in the group clinically diagnosed as cholecystitis reported by J. M. Blackford and associates.²

When the present results are compared by the same criteria with those recorded by Wilson, Lehman and Goodwin³ from the same institution, it is found that "satisfactory clinical results" are obtained in 79 per cent of cases of cholelithiasis by surgery as opposed to 43 per cent without surgery. This appears to favor surgery for cases of cholelithiasis with symptoms. On the other hand, in those with abnormal function alone on cholecystogram, the 64 per cent relief from surgery does not contrast so favorably with the 49 per cent relief without surgery. And finally, the 3.6 per cent operative mortality is about as large as the mortality from biliary causes over six and a half years in the present series.

It is not our purpose to discredit surgical treatment of gall-bladder disease, but we wish to point out that this small series of cases would again indicate: "the patient with uncomplicated cholecystitis should be given a trial on medical treatment and if not promptly relieved, he should be operated on."² Watchful waiting may obviate a major surgical procedure, and it appears to be about as safe.

SUMMARY

Ninety patients with abnormal cholecystograms were not subjected to immediate surgery. Over six and one-half years' average follow-up, the non-operative results were "satisfactory" in 47.7 per cent of the group. Satisfactory results were found in 52.5 per cent of those with poorly functioning cholecystograms, in 44.9 per cent in those with non-functioning cholecystograms and in 42.8 per cent of those with cholelithiasis.

BIBLIOGRAPHY

1. WALTERS, WALTMAN, and SNELL, ALBERT M.: Diseases of the gall bladder and bile ducts, 1940, p. 377, Saunders, Philadelphia.
2. BLACKFORD, J. M., KING, R. L., and SHERWOOD, K. K.: Cholecystitis: study based on follow-up after from five to fifteen years of two hundred patients not operated on, Jr. Am. Med. Assoc., 1933, ci, 910-913.
3. WILSON, W. D., LEHMAN, E. P., and GOODWIN, W. H.: Prognosis in gall bladder surgery, Jr. Am. Med. Assoc., 1936, cvi, 2209-2213.

HEART STRAIN: A CRITICAL REVIEW; THE DEVELOPMENT OF A PHYSIOLOGIC CONCEPT *

By AARON E. PARSONNET, M.D., C.M., F.A.C.P., and ARTHUR BERNSTEIN, A.B., M.S., M.D., *Newark, New Jersey*

MANY of the obstacles in the path of modern cardiologic progress have been swept aside in the past 50 years, and the cardiologist of today can negotiate the highways and byways of his specialty with comparative ease. His chief concern at present, therefore, is to keep these hard won pathways of knowledge clear and, from time to time, add his bit to the sum total of amassed information.

One field, however, still remains unexplored, that of heart strain. The subject is not a new one but is certainly an unsettled and misunderstood one. The law courts, insurance companies, compensation boards, industrial and military physicians, and last but not least, the cardiologists will readily attest to the consternation, conflict of opinion, involved logic, and general dissatisfaction a case of so-called "heart strain" can produce. Since this is such an important phase of cardiology and, at the same time, such a controversial one, we feel that an airing of the entire subject is long overdue.

We are presenting this work, therefore, bringing to the attention of the medical profession the accumulated evidence on both sides of the subject, with the fervent hope that by stimulating a renewed interest, all of us may be helped to a final solution of a problem which still remains unsolved.

The first source of confusion in dealing with the question of heart strain has been the lack of a comprehensive yet concise definition of the subject. The earlier writers seemed to have felt that there was no need for such a specific delineation, leaving one with the inevitable impression that heart strain differed in no way from strain of one or more of the somatic muscles. In order, then, to have a foundation for discussion, we shall define heart strain as: *That condition which produces myocardial damage, secondary to some unusual effort.* As we consider this definition, it becomes immediately apparent that this could not be applied to those cases of so-called heart strain which are supposedly due to prolonged, hard labor over many years and which the older writers, such as Allbutt, considered as the etiologic factor.¹ This then brings us to the first point that must be cleared up. Heart strain must be divided into two types, those which are produced by some sudden effort or strain, and those resulting from effort spread over a long period of time. The first we shall call "acute heart strain," and the second we shall designate "chronic heart strain." We will now consider the evi-

* Received for publication March 19, 1941.

From the Department of Cardiology, Newark Beth Israel Hospital, Newark, New Jersey.

dence for each type separately, since this has been, we feel, the basis for much of the confusion which has arisen.

Acute Heart Strain. The definition stated above seems to be most adequate for this portion of the subject, and with this in mind let us examine first the syndrome which has been covered by it before we attempt to gather evidence to prove or disprove it. The etiology of this condition, as presented by Kahn,^{2, 3} follows:

- a. *Occupations*—those causing sudden severe stress to be placed upon the heart, though these may ordinarily be light in character.
- b. *Chronic infections and intoxications*—these may act upon the myocardium and so act as an important contributory factor, though this cannot be proved.
- c. *Previously existing heart disease*—the acute strain may aggravate this condition.
- d. *Age*—this is important in that after the age of 40 there is a substitution of fibrous instead of elastic tissue, especially in the aorta, with consequent lessened elasticity and subsequently less resistance to strain.
- e. *Sex*—more common in males only because they are more often engaged in industry, though there are cases recorded in females.
- f. *The exciting cause of heart strain*—excessive exertion such as lifting, pulling, pushing, straining, stair or mountain climbing, especially while supporting a load,² coughing or laughing.⁴
- g. *Nervous strain, fatigue or excitement*—these may also cause heart lesions, but to what degree remains problematic.⁵

To summarize, therefore, we can say that acute heart strain occurs in the healthy or diseased heart, either in the male or female, when there is an unexpected sudden severe stress placed upon the heart due to some unanticipated, added physical strain thrown upon a person who is already doing almost capacity work.

The symptoms of acute heart strain are considered to be as follows³:

- a. *Onset*: To be considered, the symptoms must come on during or immediately after the performance of some strenuous work, when cardiac stress and aortic pressure are at a maximum.
- b. *Pain*: This may vary greatly and still be significant. It may be precordial or substernal in location.
- c. *Weakness*: This varies from just a disabling weakness to complete unconsciousness.
- d. *Dyspnea and palpitation*: These two symptoms occur at the time of onset of the condition and often become permanent, growing worse with time or effort.
- e. *Disability*: The cardiac response is definitely limited after an acute strain, with any exertion producing marked cardiac symptomatology.

- f. *Heart failure*: If the patient continues to work, the symptoms of heart failure often ensue.
- g. *Death from primary heart strain*: This occurs as a rule only when some preëxisting cardiac pathologic lesion is aggravated by the strain.

Almost the same set of symptoms for acute heart strain is listed by Peacock, emphasizing the fact that when this condition is seen, it is fairly characteristic within certain wide limits.⁶

The physical findings in the typical case are extremely variable, as is to be expected. These vary from simple tachycardia to complete collapse³:

- a. Rapid pulse rate, usually with a small pulse.¹
- b. Auricular fibrillation often occurs at once with frequent recurrences.⁴
- c. Irritable heart with its attendant symptoms may be found.⁷
- d. Murmurs at one or another of the valve areas which may be due either to rupture of the valve, or to functional changes after the severe strain.^{5, 6}
- e. Cardiac dilatation may be found at times.²
- f. Tender spots may be found on the chest wall over the precordium.³
- g. Various arrhythmias other than fibrillation may also be found after an acute strain, such as extrasystoles, flutter and paroxysmal tachycardias.⁵
- h. The electrocardiogram may show various changes in the T-waves, such as inversion in various leads, and at times even bundle branch block is seen.^{3, 5}

In the course of time there will, of course, occur certain changes which will depend largely upon the seriousness of the original damage. When heart failure supervenes its set of symptoms must be added to the others.

Having outlined these criteria of acute heart strain as a basis for discussion let us examine the literature both for and against such a concept. Allbutt was impressed by the fact that in a large laboring population many of the young, healthy males had heart ailments, and upon close observation he became convinced that strain of effort was the common factor at the root of these cardiac difficulties. He felt that overstretching of the heart muscle fibers beyond their physiologic limits could cause alterations of the molecular structure of the fibers, thereby producing a permanent damage that would be progressive in character.¹ Bainbridge, although he admits the difficulty of scientific proof, agrees with this theory. However, he does straddle the fence somewhat, since he limits such strain to middle life or to postinfectious states when there has already been some impairment of the myocardial circulation.⁸ Eyster, from his experimental work in increasing the load on the heart of dogs by placing constricting bands about their aortas for varying lengths of time, concludes that cardiac hypertrophy that develops in organic heart disease is not owing to the increased work of the muscle per se, but to the muscle injury and the reaction to the injury that result

from the abnormal stretching of the muscle in the initial period of the overload. He states further that the overload upon the heart need last but a very short time in order to produce muscle injury which will later allow hypertrophy and failure to develop. In spite of these findings in his work upon animals, Eyster does not feel that the same condition can occur in man unless there has been some cardiovascular disease already present prior to the load being placed upon the heart.⁹ This statement further emphasizes the state of confusion in which we find ourselves whenever heart strain is the subject of discussion. Although all the experimental work seems to point toward the existence of such an entity, Eyster denies this because of his normal heart findings in a group of athletes. The experimental work showing that heart muscle injury does occur after an undue load has been placed upon the heart, with resultant heart failure subsequently, is certainly convincing enough. The question of the athlete's heart will be discussed in a later chapter.

Clinically, on the other hand, many observers felt that acute heart strain can and does occur. Peacock, in 1865, presented several cases to prove his contention that cardiac strain resulted when sudden stress was thrown upon the heart.⁶ Allbutt proposed much the same concept.¹ DaCosta, in his now historical article on the irritable heart, speaks of heart strain as a true entity.⁷ Kaufmann, in his equally careful studies, found that cardiac enlargement can and does occur after exertion.¹⁰ Hay and Jones were particularly interested in the development of auricular fibrillation as a result of heart strain and quote several cases to illustrate their point.⁴ The Kahns, in their several papers on this subject, have, of course, presented a very complete brief for the concept of heart strain.^{2, 3, 11} They have painstakingly reviewed the literature and present most convincingly arguments in defense of their conclusions and cite many cases of their own as well as those of others to substantiate their rather positive and at times dogmatic views. Christian says that strain may cause subsequent cardiac hypertrophy and then dilatation.¹² White and Glendy, in their chapter on "Trauma and Heart Disease," in Brahdry and Kahn's recent book, state that their review of the literature also makes them feel that heart strain is one of the forms of trauma which is capable of producing cardiac damage.⁵

This presents but a short summary of the opinions of those men who have contributed the most outstanding papers upon the affirmative side of the question as to whether there is a clinical entity which can be designated as heart strain and which, in turn, is capable of producing cardiac damage of a nature severe enough to result in a fatal termination in many instances.

There is, of course, an equally emphatic group which is entirely opposed to the above concept. Gordon and Strong exercised normal rabbits and those whose hearts had been enlarged by the use of adrenalin and spartein sulfate, until the animals were exhausted, and found a contraction of their heart size, in the exhausted state, of about 19 per cent. (The weight silhouette method was used to determine heart size before and after exercise.)

The animals all recovered within a short space of time and seemed to have suffered no ill effects at the end of a two-month observation period. Gordon and Strong conclude, therefore, that exercise causes the heart to get smaller and so there could be no heart strain.¹³ This question of exercise and its effect upon heart size will be discussed later and the fallacy of the above argument shown.

Barron says that the normal heart does not increase in size, no matter how great the load that is placed upon it. However, he goes on to say that when the myocardium has been weakened by disease, then a load may be placed upon it which will exceed the physiologic limit of the muscle, producing a dilatation. This in turn causes weaker muscular contractions, with lessened efficiency and subsequent further dilatation and finally failure.¹⁴

Sir Thomas Lewis has been the greatest opponent of the theory of heart strain. He feels that the heart cannot dilate beyond physiologic limits because of the fibrous pericardium. He summarizes his views by stating "if strain of the healthy heart exists, it is no more than a curiosity."¹⁵ In some of his later work he does, however, feel that valve cusps may rupture during violent body effort with resultant dilatation of the heart. Yet even here he presupposes that the heart was not healthy to start with.¹⁶

This, in substance, is the evidence for and against the concept of acute heart strain. We can readily see that the question resolves itself into the weight of authority as represented by Sir Thomas Lewis on the one side, as against the weight of clinical evidence in favor of the entity. Lewis places all his emphasis upon the fact that the heart muscle can withstand any strain so long as it is not already diseased. It is pertinent to point out here that all the workers in favor of the concept have kept this precept in mind and have carefully checked each of their cases to rule out such a possibility, yet they still felt that they found cases of heart strain clinically. Therefore, on the basis of the work of these clinical investigators, coupled with our own experience, we conclude that acute heart strain is a distinct and well-defined clinical syndrome. In this connection, let us see whether we can refute Lewis's arguments against the concept so that we will also be able to strengthen our cause on a theoretical basis as well.

The animal work of Eyster, which was previously quoted, showed very conclusively that a load thrown upon the healthy heart, even for a relatively short time, is capable of causing damage sufficient to produce subsequent failure. Though the strain thrown upon the hearts of these animals was not quite comparable to that seen in acute heart strain, there is enough similarity in that it proves very definitely that the healthy heart may be damaged by a sufficiently severe load.⁹ This work pretty definitely shows that enough of a strain can be thrown upon heart muscle to damage the fibers so that hypertrophy and finally cardiac failure will ensue. In this way Lewis's chief argument becomes untenable.

Not only in animals may we demonstrate the fact that rupture of the cardiac muscle may occur; there are many references in the literature to

cases of rupture of the human heart muscle, of the valve cusps, the development of arrhythmias, as the result of mild blows upon the chest, or even indirectly from trauma localized in the abdomen or parts of the body other than the chest.^{5, 11, 17, 18, 19, 20, 21, 22, 23} Autopsies on several of these patients show that the rupture occurred through a portion of the myocardium which appeared to be normal in every way except for the rent in it.^{18, 19, 20} Bilderbeck, citing one of his cases, advanced the suggestion that the probable cause of the heart rupture was the sudden compression of a right auricle which became engorged due to the patient holding his breath in deep inspiration just before the blow struck.¹⁹ The same view is presented by Glendy and White, who feel that an important factor in heart wall rupture is the distention of the heart chamber at the end of diastole or the beginning of systole; at this time any sudden or extreme pressure is far more apt to cause the heart to rupture whether it is diseased or not.⁵ Lewis himself records the fact that when a deep inspiration is taken with the glottis closed the heart is seen to dilate very markedly and remain in this state as long as the inspiration is maintained, though it invariably will return to normal when the breath is released.¹⁶

With these facts in mind let us picture a man lifting a weight which is at about the limit of his capacity; his every muscle is strained, his neck veins are engorged, and in all likelihood he is holding his breath (the picture presented by Lewis). Suddenly this man slips, or the load teeters, or something else happens which demands an added sudden effort. May we not then conceive that with the heart already distended, the increase in pressure brought on by that sudden added effort adds the last straw, and there is a rupture of some of the muscle fibers, or else there may be a rupture of a small blood vessel with resultant myocardial damage. After such heart muscle has once been damaged, further changes may occur.

Harrison says that if increase in heart fiber size is due to increased load on that fiber, then increased work of the heart as a whole, or disease of other fibers would throw a greater burden on the sound fibers with resultant hypertrophy. Dilatation then results when the hypertrophy fails adequately to take care of the increased demands upon the heart.²⁴ Willius and Smith, and Thompson and White feel much the same way about the causes of hypertrophy and dilatation.^{25, 26} So then, in the acute strain, after the fibers are damaged, if it is severe enough, there will be an added burden thrown upon the sound fibers with hypertrophy and then failure. This then is the probable explanation of why Eyster's dogs showed cardiac changes long after the load had been removed.⁹

Let us assume, however, for the sake of argument, that Lewis is right, and it is impossible to tear a heart muscle fiber. Could we still explain the occurrence of acute heart strain? The answer is yes. There is enough evidence in the literature to show that one may get a relative coronary insufficiency with ischemia and anoxemia of a portion of the myocardium. The man who is working at full capacity, and who then adds a little more to his

exertion, may suddenly find himself with an inadequate blood supply to a portion of his myocardium with resultant changes identical in every respect to those seen after a coronary occlusion or thrombosis. The sequence of events after such an occurrence can be just as varied as those seen after a true occlusion.²⁷

There is some experimental work which shows pretty definitely that by distending the left ventricle one may produce arrhythmias of variable kinds, especially ventricular tachycardias.²⁸ Once a tachycardia is established it is simple to conceive of either a ventricular fibrillation occurring, or with a reduced cardiac output due to the shortened diastolic period, a relative coronary insufficiency ensuing. Since we know that there can be overdistention of the ventricle in heart strain, as previously pointed out, this series of events can also be anticipated.

We have, then, enough evidence to show that a man who is working at his limit of capacity, may, by a sudden added exertion, produce damage to his heart in one of several ways.

In summary, therefore, we may say that our definition of acute heart strain as "that condition which produces myocardial damage, secondary to some unusual effort," can be justified on the bases of both experimental and clinical work. Clinically, it is a condition in which substernal or precordial pains come on suddenly during an *unusual effort*, producing certain changes which can be determined objectively. If this concept is kept in mind, we shall have an entity which can thus be recognized.

Chronic Heart Strain. Having presented the picture of acute heart strain, we shall now carefully consider the other phase of the question, i.e., chronic heart strain. Though many have dealt with this concept since Allbutt first discussed it, no one seems to have crystallized the thought conveyed by the phrase.¹ We shall, therefore, define the idea as presented by the various authors who have been much interested in this topic. For the sake of argument, chronic heart strain may be defined as an *organic condition, associated with the sudden or gradual onset of symptoms referable to the cardiovascular system which can be attributed to severe muscular effort over a long period of time, resulting in physical disability of varying degree and duration.* It is self-evident that this definition leaves out a great deal that is important and is, therefore, open to severe criticism. However, this seems to be the only definition that will adequately cover the concept as most authors present it. Having defined the subject, we may now proceed to a consideration of the etiologic factors:

- a. *Occupations*—any one which demands prolonged heavy exertion.^{1, 3, 6}
- b. *Athletics*—running, swimming, weightlifting, and rowing.^{1, 22}
- c. *Age.*³

In other words, any heart which is subjected to full capacity demands at frequent intervals, for long periods of time, either because of occupation or avocation, is likely to begin to fail owing to the chronic strain placed upon it.

The physical findings of cardiac failure are too well known to need repetition here.

The pathology here seems to be quite definite. The following are the most important findings²:

- a. Atheroma of the aorta and arteriosclerosis.
- b. Hypertrophy of the heart.
- c. Cardiac dilatation.
- d. Coronary artery disease.
- e. Aneurysm of the left ventricle.
- f. Aneurysm of the aorta.
- g. Temporary diminution of tone or contractile power of the heart, as seen after fatigue.

Allbutt gives much the same picture of the pathology of this condition in his paper.¹

At this time let us once more "examine the record" and decide whether we are dealing with an entity or not. The Kahns feel very definitely that chronic stress plays havoc with the myocardium and leads to failure.³ Allbutt found many examples of heart disease in "young, well-made subjects of healthy build, and previously unaffected by constitutional disease." "After a time," he says, "I became convinced of the part played by mechanical causes in a large number of these patients."¹ Peacock also thought that heavy laborers showed diseases of the heart more often than others.⁶ Dietlen called attention to the fact that soldiers had larger hearts than the general population, owing, he thought, to the severe military drills and enforced marches.²⁹ Schieffer, in several articles, pointed out that soldiers' hearts became larger after a year in service, especially if they had never done hard work in their civilian life^{30, 31, 32, 33}; in addition, he observed that military bicycle riders of three or more years' service showed a definite increase in cardiac size. Furthermore, men in the heavier industries showed larger hearts than their fellows. Maase and Zondek,³⁴ and Klewitz,³⁵ in their more or less similar studies upon the military, found that infantrymen who had engaged in long marches had larger hearts than those who had not.

The athlete has also contributed his share to the controversy, since it was felt that the man engaging in competitive sports for any length of time, either as a professional or as an amateur, should certainly exhibit signs of chronic heart strain. Before discussing this particular phase of the problem, let us digress a bit and attempt to settle an issue that tends to add confusion to an already snarled subject. As previously stated, Gordon and Strong, as well as many others, found the hearts of rabbits and athletes to be either normal or slightly smaller than normal when checked after violent exertion.^{13, 36, 37,}

^{38, 39, 40, 41, 42, 43} As was to be expected, these findings have aroused much comment, speculation and free theorization. Albu, in studies made on wrestlers, discovered that at the end of one minute of the contest there was no change in heart size; at the end of five minutes the heart was smaller, and

at the end of 10 minutes it was larger.⁴⁴ Bruns' work showed that there was diminution in heart size following exertion, but that during the actual effort the results were uncertain, showing at times an increase and at other times a decrease in heart size.⁴⁵ Moritz tried to explain this phenomenon by the fact that the shortened diastole produced a lessened filling and hence a smaller heart.³⁷ Hoffman blamed the changing position of the diaphragm for giving a false impression of heart size, thus confusing the observer into believing that the heart size really changed.³⁶ The most plausible explanation, however, is that given by Bainbridge. He says that immediately after exercise the venous return to the heart is cut down most abruptly owing to the cessation of the muscle pumping action, whereas the heart rate remains elevated for some time, thereby creating a period during which the cardiac output exceeds the inflow, thus resulting in a diminution of heart size.⁴⁶ This explains quite clearly the reason why various workers have found the hearts to be smaller in subjects studied immediately after violent exercise. The cardiac dilatation during exercise, as pointed out by Albu,⁴⁴ and Bruns,⁴⁵ is physiological since the heart must, in an effort to increase its output per beat, dilate in accordance with the "law of the heart" to increase its contractile power. We may reasonably conclude, therefore, that the question of heart size immediately following exercise plays no part in our present discussion of heart strain.

We shall now return to the question of whether athletic pursuits over long periods of time are instrumental in the production of chronic heart strain. Deutsch and Kauf, who have done most extensive work on heart size in athletes, found that only oarsmen, swimmers and skiers showed cardiac enlargement of any appreciable degree. It is interesting to note that they found a familial tendency to larger hearts where they studied various members of the same family engaged in various sports for varying lengths of time. Those athletes who were observed for many years showed extremely diverse results. However, the authors did note that once the heart enlarged on exercise, even though it later became smaller, such hearts were more likely to become enlarged upon effort.⁴⁷ Again it must be pointed out here that such enlargement may have been only a work hypertrophy, for the figures given by Deutsch and Kauf do not point to true pathologic dilatations.

Since the old adage that "whatever the animals do must be natural," is accepted by many, it is of interest to look into some of the experiments dealing with them. Bergmann found that wild animals have larger hearts than household pets, owing, he thought, to the greater activity engendered by their wild state.⁴⁸ The birds that fly farther in their migrations have the bigger hearts, according to the researches of Parrot.⁴⁹ Grober compared the hearts of the wood hare, the wild rabbit and the pen rabbit. The wood hare had a heart that weighed three times that of the wild rabbit of the same body weight, and these hearts weighed more than those of the pen rabbits. In the duck family, the heart of the wild duck was heavier than that of the domesticated fowl.⁵⁰ Lastly, the frizzle fowl, that peculiar creature of an

even more peculiar name, with a markedly elevated metabolism and a heart rate of 100 beats or more per minute, more than that of ordinary chickens, also has a heart that is significantly heavier.⁵¹ But here also the enlargement found may be explained upon the basis of physiologic work hypertrophy and need not be considered as truly pathologic or regarded as proof of damage to the heart by work.

In refutation of the chronic heart strain concept, we also possess a certain amount of valid work. Kahn, in a survey of the underlying factors of angina pectoris, restates the fact that those in strenuous occupations are less likely to experience attacks of angina pectoris, which he feels is owing to the fact that such hearts become accustomed to the strain of constant effort, whereas the hearts that have never been worked very hard are immediately injured when a sudden severe strain is put upon them.⁵² Lewis, of course, is firmly arrayed against the concept of chronic strain. He points out that the enlargement seen in heavy laborers is entirely physiologic, due to a work hypertrophy which is not pathological, and that its counterpart is exhibited by the biceps and other muscles of the body as well.¹⁰ Certainly, the marathon runner should be considered a heavy laborer from the point of view of chronic stress; yet, in studying a group of men who had been marathoners for from five to 15 or more years, Gordon could find no cardiac enlargement, using the cardiothoracic ratio or the transverse diameter figures as criteria for analysis.⁵³ Another argument against the chronic strain concept is the transcontinental derby. Farrel studied 23 runners three days after they had reached New York from Los Angeles. These men had averaged 40 miles daily for 84 consecutive days, yet only one of this group had an enlarged heart and that was the heart of a 64 year old, short, stocky individual who had been running for 40 years.⁵⁴ The cardiothoracic ratio of Danzer was used as a means of comparison.⁵⁴ When the tables of Bardeen were used five hearts showed greater diameters than the predicted ones.⁵⁴ Nevertheless, the authors concluded that the immediate effects of this long distance run were inconsequential.⁵⁴ It is well to recall that Deutsch and Kauf also found very few cardiac enlargements in their group of seasoned athletes.⁴⁷ Finally, White and Glendy, after a careful review of the literature, state that the constant strain of hard, physical work has never been proved to be the cause of myocardial disease.⁵

As we look back upon the material presented, we find that a preponderant volume of literature favors the concept of chronic heart strain as an entity, but a careful analysis of the literature makes it impossible for us to subscribe to the theory. In the first place, the etiology, pathology and symptomatology of the condition are practically those of arteriosclerotic heart disease, which we would expect to find in this age group anyway. Therefore, in any given case we are immediately confronted with the exceedingly difficult task of deciding whether the changes found are those owing to chronic heart strain or to arteriosclerosis from some other and entirely unrelated cause. This fact alone makes us wonder how many cases are labeled

chronic heart strain when they are merely showing to a lesser or greater degree the inexorable signs of "physiologic" sclerosis. Allbutt and Peacock based their impressions upon clinical observations over long periods of time.^{1, 6} Keen observers though they were, one may nevertheless wonder how many of their cases were suffering from undiagnosed rheumatic fever, postinfectious myodegeneration, congenital heart defects, or from malnutrition and avitaminosis, all of which may eventually lead to the cardiac breakdown.

How then may we reconcile the facts that soldiers' hearts are larger than those of civilians, and messengers' hearts larger than those of ordinary soldiers, and the hearts of frizzle fowl larger than those of ordinary chickens? Lewis points out that the physiology of muscle is such that the cardiac musculature must hypertrophy with use within certain physiologic limits.¹⁶ This will adequately answer all the questions raised in the introductory sentence of this paragraph. Furthermore, though the heart of the frizzle fowl is larger than that of the chicken, owing to its increased work, all frizzle fowl do not die of cardiac dilatation and failure, and neither do the wild rabbits or the soldiers. In other words, even though there is a work hypertrophy, subsequent dilatation and failure is not the rule nor is it even a common finding. Practically applied it means that the man who works hard all his life may have a heart that is larger than that of his desk-sitting contemporary, but this is entirely owing to a physiologic muscle development and not to a beginning myocardial damage with subsequent dilatation and failure.

Therefore, though the volume of words in support of chronic heart strain is preponderant, careful analysis of the material tends to invalidate most of it, leaving us with the logical conclusion that the concept of chronic heart strain is unsupported by scientific proof and as an entity is non-existent.

Somewhat timidly we are inserting the following paragraph of pure speculation, hoping that it will not confuse the picture which we trust has been somewhat clarified by this work.

Since the men in heavy industry are more likely to suffer an acute heart strain by the very nature of their work, we wonder how many of them do receive an acute strain which is overlooked and subsequently forgotten? Then, several months or years later, they suddenly begin to decompensate. How many of such instances, since there seems to be no other explanation, have been attributed to chronic heart strain? In other words, we raise the question as to how many cases of acute heart strain have gone unrecognized and the end results labeled chronic heart strain for the lack of a better appreciation of what had actually occurred. So rather than jump at conclusions and use the meaningless term of chronic heart strain in the face of a case of sudden decompensation in a heavy worker, it might be far wiser to look for an acute heart strain in his past history. *Not finding such a history, the presence of heart strain is to be absolutely excluded.*

We have attempted in this paper to establish only a basis for future work. No effort has been made to consider, as yet, the medico-legal significance of

our concepts or their application to industry. It has been our aim, so far, only to help the doctor diagnose and so treat the patient presenting himself with "a strained heart." The application of these principles to "heart strain" in industry is a question which is worthy of a separate discussion.

SUMMARY

1. Heart strain is divided into acute and chronic types with definitions for each as a basis for discussion.
2. After a survey of the literature pro and con, it is felt that a clinical entity of acute heart strain can be justifiably established.
3. Theories as to the mechanism of acute heart strain are outlined.
4. The concept of chronic heart strain is considered to be too vague and uncertain and too lacking in confirmatory evidence to be established as an entity at all. It is felt that this term should be dropped since it is misleading as well as a misnomer.
5. The question of the heart in athletics is also considered from the point of view of heart strain.

BIBLIOGRAPHY

1. ALLBUTT, T. C.: The effects of overwork and strain on the heart and great blood vessels, St. George's Hosp. Rep., 1870, v, 23.
2. KAHN, M. H., and KAHN, S.: Heart strain and its consequences, ANN. INT. MED., 1928, i, 790.
3. KAHN, M. H., and KAHN, S.: Heart strain and its industrial aspects, Am. Heart Jr., 1928, iii, 546.
4. HAY, J., and JONES, H. W.: Trauma as a cause of auricular fibrillation: its medicolegal significance, Brit. Med. Jr., 1927, i, 559.
5. WHITE, P. D., and GLENDY, R. E.: In Trauma and disease, by BRAHDY, L., and KAHN, S., 1937, Lea & Febiger, Philadelphia, pp. 24-78.
6. PEACOCK, T. B.: Valvular disease of the heart, 1865, Churchill & Sons, London, p. 34.
7. DA COSTA, J. M.: On irritable heart; a clinical study of a form of functional cardiac disorder and its consequences, Am. Jr. Med. Sci., 1871, lxi, 2.
8. BAINBRIDGE, F. A.: The physiology of muscular exercise, 1919, Longmans, Green & Co., New York, pp. 198-201.
9. EYSTER, J. A. E.: Experimental and clinical studies in cardiac hypertrophy, Jr. Am. Med. Assoc., 1928, xci, 1881.
10. KAUFMANN, R.: Ueber die Häufigkeit und Art der Herzscheidigungen bei Rückkehrenden Frontsoldaten, München. med. Wchnschr., 1916, lxiii, 1164.
11. KAHN, M. H., and KAHN, S.: Cardiovascular lesions following injury to the chest, ANN. INT. MED., 1929, ii, 1013.
12. CHRISTIAN, H. A.: Chronic nonvalvular heart disease—its causes, diagnosis, and management, California and West. Med., 1930, xxxii, 320.
13. GORDON, B., and STRONG, G. F.: Studies on the rabbit's heart. II. Effect of vigorous exercise on the size of the normal and the abnormal heart, Arch. Int. Med., 1923, xxxii, 517.
14. BARRON, M.: Cardiac decompensation and its treatment, Minnesota Med., 1929, xii, 487.
15. LEWIS, T.: The soldier's heart and the effort syndrome, 1933, P. B. Hoeber, New York, pp. 27-40.
16. LEWIS, T.: Diseases of the heart, 1933, The Macmillan Co., New York, pp. 151-157.

17. PEACOCK, T. B.: Case of rupture of right ventricle of the heart, *Trans. Path. Soc.*, 1880, xxxi, 72.
18. GIBBONS, J. B.: Rupture of the heart by a blow with a stick, *Indian Med. Gaz.*, 1897, xxxii, 443.
19. BILDERBECK, A. C. L.: Traumatic rupture of the heart without fracture or external lesions, *Brit. Med. Jr.*, 1919, i, 675.
20. SAPHIR, O.: Rupture of the heart by indirect trauma in a four-year-old boy, *Am. Jr. Med. Sci.*, 1927, clxxiii, 353.
21. LEVISON, L. A.: The relation of trauma to cardiac disease, *ANN. INT. MED.*, 1927, i, 227.
22. KAHN, M. H.: Auricular flutter following direct injury to the chest, *Am. Jr. Med. Sci.*, 1930, clxxix, 605.
23. KRUMBHAAR, E. B., and CROWELL, C.: Spontaneous rupture of the heart, *Am. Jr. Med. Sci.*, 1925, clxx, 828.
24. HARRISON, T. R.: The newer knowledge of heart disease. IV. The causes of heart failure, *South. Med. Jr.*, 1929, xxii, 1009.
25. WILLIUS, F. A., and SMITH, H. L.: Factors concerned in cardiac hypertrophy, *Am. Heart Jr.*, 1934, x, 190.
26. THOMPSON, W. P., and WHITE, P. D.: The commonest cause of hypertrophy of the right ventricle—left ventricular strain and failure, *Am. Heart Jr.*, 1936, xii, 641.
27. BLUMGART, H. L., SCHLESINGER, M. J., and ZOLL, P. M.: Angina pectoris, coronary failure and acute myocardial infarction, *Jr. Am. Med. Assoc.*, 1941, cxvi, 91.
28. KISCH, B., GOLDBLOOM, A. A., and ZUCKER, G.: Influence of increased ventricular pressure on the electrocardiogram, *Meet. New York Heart Assoc.*, Feb. 25, 1941.
29. DIETLEN, H.: Ueber Grösse und Lage des normalen Herzens und ihre Abhängigkeit von physischen Bedingungen, *Arch. f. klin. Med.*, 1906, clxxxviii, 55.
30. SCHIEFFER, K.: Ueber den Wert der Orthodiagraphie als diagnostische Hilfsmittel mit besonderer Berücksichtigung der Herzuntersuchungen der Soldaten, *Deutsch. mil. ärztl. Ztschr.*, 1906, xxxv, 589.
31. SCHIEFFER, K.: Ueber Herzvergrößerung infolge Radfahrens, *Deutsch. Arch. f. klin. Med.*, 1907, lxxxix, 604.
32. SCHIEFFER, K.: Ueber dem Einfluss der Berufsarbeit auf die Herzgrösse, *Ibid.*, 1908, xcii, 383.
33. SCHIEFFER, K.: Ueber dem Einfluss des Militärdienstes auf die Herzgrösse, *Ibid.*, 1908, xcii, 392.
34. MAASE, C., and ZONDEK, H.: Herzbefunde bei Kriegsteilnehmern, *Ztschr. f. klin. Med.*, 1918, lxxxix, 391.
35. KLEWITZ, F.: Berufsarbeit und Herzvergrößerung bei Frontsoldaten, *München. med. Wchnschr.*, 1918, lv, 927.
36. HOFFMANN, A.: Gibt es eine schnell vorübergehende Vergrößerung des normalen Herzens? *Verhandl. XX Kongr. f. inn. Med.*, 1902, 302.
37. MORITZ, F.: Ueber funktionelle Verkleinerung des Herzens, *München. med. Wchnschr.*, 1908, lv, 713.
38. LENHOFF, R., and LEVY-DORN: Untersuchungen an Ringkämpfern, *Deutsch. med. Wchnschr.*, 1905, xxxi, 869.
39. MENDEL, J., and SELIG, A.: Zur Frage der akuten Herzdilatation, *Med. Klin.*, 1907, iii, 135.
40. KIENBOCK, R., SELIG, A., and BECK, R.: Untersuchungen an Schwimmern, *München. med. Wchnschr.*, 1907, liv, 1427, 1486.
41. DIETLEN, H., and MORITZ, F.: Ueber das Verhalten des Herzens nach langdauerndem und anstrengendem Radfahren, *München. med. Wchnschr.*, 1908, x, 489.
42. JUNDALL, I., and SJORGEN, T.: Röntgenologische Herzgrössenbefunde bei Ringern, *Nord. med. ark.*, 3F, 1912, xii, 1.

43. KATZ, L., and LEYBOFF, M.: Röntgenologische Herzgrössebestimmungen an Ringern, Deutsch. med. Wchnschr., 1913, xxxix, 1589.
44. ALBU, A.: Die Wirkung körperlicher Ueberanstrengung beim Radfahren, Berl. klin. Wchnschr., 1897, xxxiv, 202.
45. BRUNS, O.: Untersuchungen über Herzgrösse, Blutdruck und Puls vor, während und nach kurzdauerender, starker körperlicher Arbeit, München. med. Wchnschr., 1921, lxviii, 907.
46. BAINBRIDGE, F. A.: The physiology of muscular exercise, 1919, Longmans Green and Co., New York, pp. 57-63.
47. DEUTSCH, F., and KAUF, E.: Heart and athletics, 1927, C. V. Mosby Co., St. Louis.
48. BERGMANN, J.: Ueber die Grösse des Herzens bei Menschen und Tieren, München, 1884.
49. PARROT, G.: Ueber die Grössenverhältnisse des Herzens bei Vögeln, Inaug.-Diss. München, 1893, Zool. Jahrb. 1894, 7.
50. GROBER, J.: Beziehungen zwischen Körperarbeit und der Masse des Herzens und seiner Teile, Arch. f. exper. Path. u. Pharm., 1908, lix, 962.
51. BOAS, E. P., and LANDAUER, W.: The effect of elevated metabolism on the heart of frizzle fowl. II. Increased ratio of heart to body weight, Am. Jr. Med. Sci., 1934, clxxxviii, 359.
52. KAHN, M. H.: Etiologic factors in angina pectoris, Am. Jr. Med. Sci., 1926, clxxii, 195.
53. GORDON, B., LEVINE, S. A., and WILMAERS, A.: Observations on a group of marathon runners, Arch. Int. Med., 1924, xxxiii, 425.
54. FARRELL, J. T., JR., LANGAN, P. C., and GORDON, B.: A roentgen study of a group of long-distance runners, Am. Jr. Med. Sci., 1929, clxxvii, 394.

THE RELATIONSHIP OF UPPER RESPIRATORY INFECTIONS TO RHEUMATIC ACTIVITY IN CHRONIC RHEUMATIC HEART DISEASE*

By IRVING R. JUSTER, M.D., F.A.C.P., *Glens Falls, New York*

CLINICAL manifestations of rheumatic fever had long been known to follow infections of the upper respiratory tract. This sequence of events gave rise to the concept that these infections were etiological,^{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12} particularly those having a predominance of hemolytic streptococci.^{7, 8, 9, 10, 11, 12, 13} Several investigators, however, were unable to substantiate such a relationship even with regard to hemolytic streptococcus infections,^{14, 15, 16, 17, 18, 19, 20} and some maintained that recurrences occurred more frequently without prior infections.^{14, 15, 16, 19, 21, 22, 23, 24, 25, 26, 27} Furthermore, Bland and Jones²² showed that the incidence of recurrences following operations, accidents and vaccine injections was similar to that occurring after upper respiratory infections. Although a relationship was highly suggestive, Swift^{28, 29, 30} and others³¹ were of the opinion that it still was not definitely proved. Swift³² and others^{33, 34} also demonstrated that a hypersensitive state existed in rheumatic subjects and that infections tended to increase it.^{29, 30, 32, 35, 36, 37} The hypersensitive state, however, was not limited to bacterial filtrates, for the same reaction was observed to rabbit serum.³⁸ Coburn and Pauli,¹⁰ the staunchest advocates of the etiological significance of hemolytic streptococcus infections, did not consider them the only factor underlying the development of rheumatic fever. Rinehart and his coworkers^{39, 40} believed that vitamin C deficiency was the added factor, but Swift²⁸ could not prevent recurrences of the disease by active treatment with vitamin C. Rheumatic recurrences developing under such varied circumstances suggested the existence of an unrecognized factor or factors. It is obvious from these divergent views that the etiology of rheumatic fever is not yet definitely known.

It has been previously shown in this group of ambulatory rheumatic cardiac patients that active rheumatic infection was present in several cases and led to progressive cardiac damage and diminished cardiac reserve without the appearance of clinical manifestations of the disease; whereas, in others, a preëxisting active process was often noticed prior to the development of recurrences. These subclinical periods of rheumatic activity were recognized chiefly by the presence and persistence of leukocytosis.^{41, 42} Be-

* Received for publication March 31, 1941.

This is the fourth of a series of four articles on investigations undertaken at the New York Cardiac Shop, conducted under the auspices of the Committee on Cardiac Clinics of the New York Heart Association. This study was made possible by grants from the Hofheimer Foundation for three years, the New York Foundation for two years, and the Altman Foundation for one year. The remainder of the fund was subscribed by the Board of Directors of the New York Cardiac Shop. This Board was created by the Board of Directors of Irvington House.

cause of this experience it was deemed advisable to ascertain whether upper respiratory infections initiated rheumatic activity or complicated a pre-existing active process.

Seasonal Incidence of Upper Respiratory Infections. During the three-year period of observation 85 per cent of the patients experienced a total of 216 upper respiratory infections. The seasonal incidence showed a high prevalence in winter, a decline in summer and another period of high prevalence in fall (figure 1). These findings were in accord with those of Wilson et al.¹⁴ and others observing non-rheumatic subjects.^{43, 44, 45, 46}

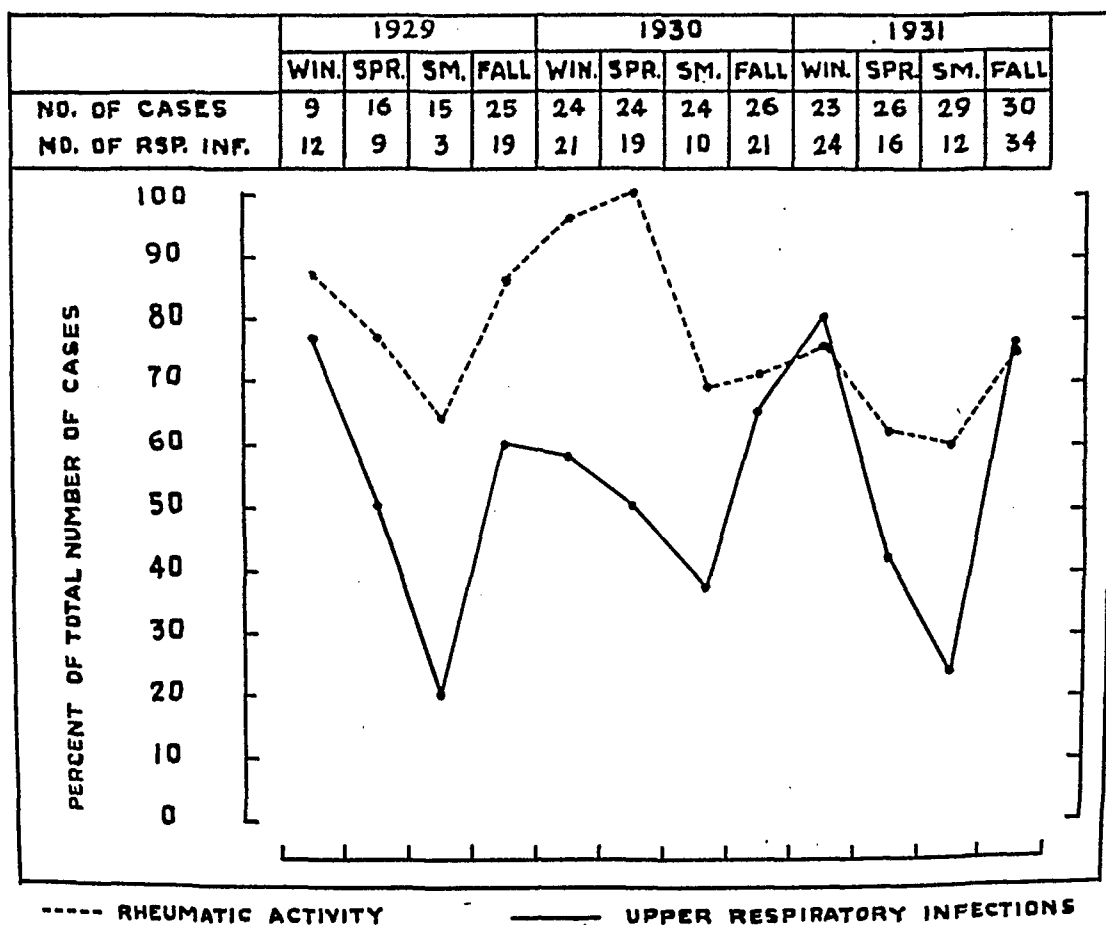
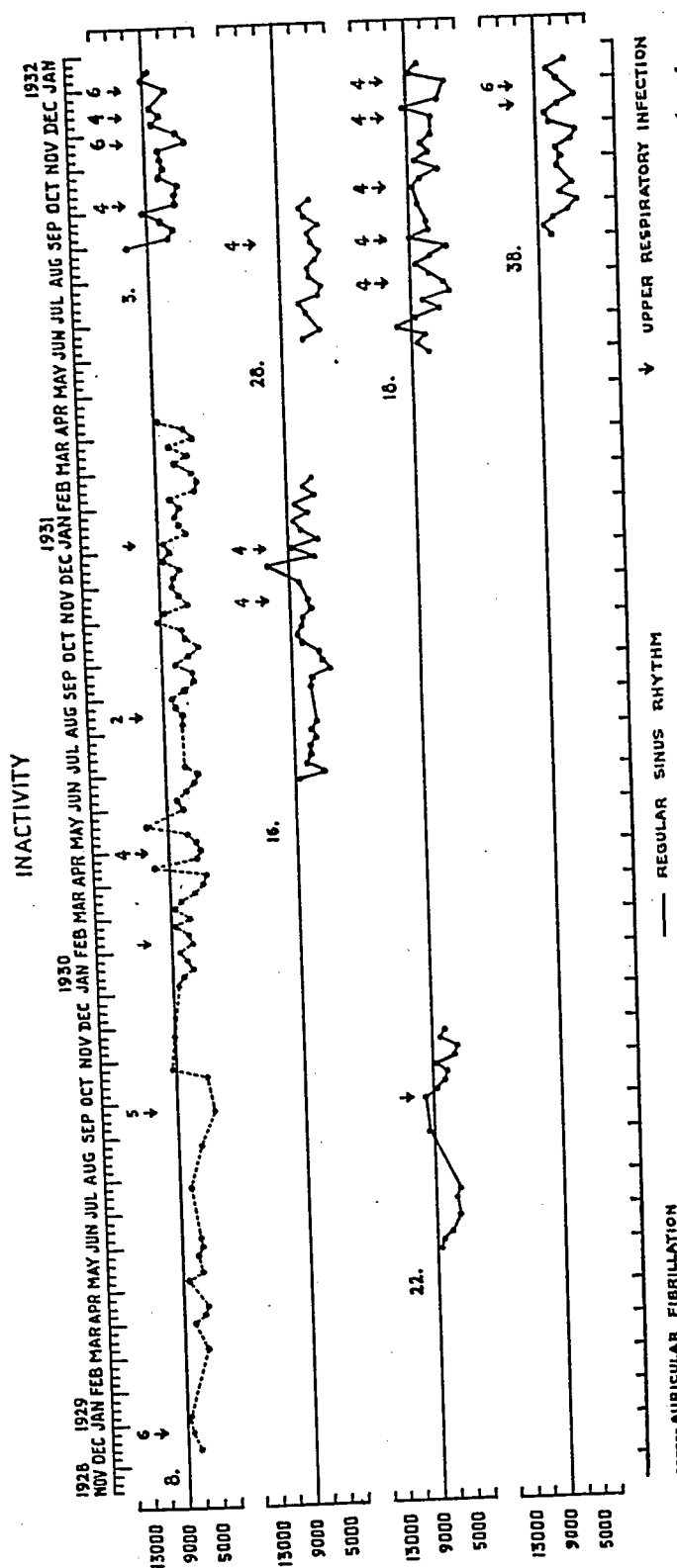


FIG. 1. Seasonal incidence of upper respiratory infections and rheumatic activity (first, second and third degrees, combined).

Upper respiratory infections per se are of doubtful significance as an etiological factor, since they occur with the same frequency in rheumatic and non-rheumatic subjects.

Seasonal Incidence of Upper Respiratory Infection and Rheumatic Activity. Rheumatic activity based on the classification previously proposed⁴² was determined seasonally and compared with the seasonal incidence of upper respiratory infections (figure 1).

During 1929 the curves were parallel; during the winter of 1929-30 and spring of 1930 they diverged, becoming more or less parallel thereafter.



-----AURICULAR FIBRILLATION

FIG. 2. Arrows designate upper respiratory infections in relation to weekly leukocyte counts. Arrows with numerals above designate upper respiratory infections and the number of days after the weekly leukocyte counts. Numerals at the beginning of each curve designate case numbers.

The parallel course of the curves suggested a causal relationship, whereas the divergent course did not. From the fall of 1929 to the spring of 1930 rheumatic activity increased (80 per cent to 100 per cent), whereas upper respiratory infections dropped (60 per cent to 48 per cent). Furthermore, from the fall of 1930 to the winter of 1931 there was a marked increase of

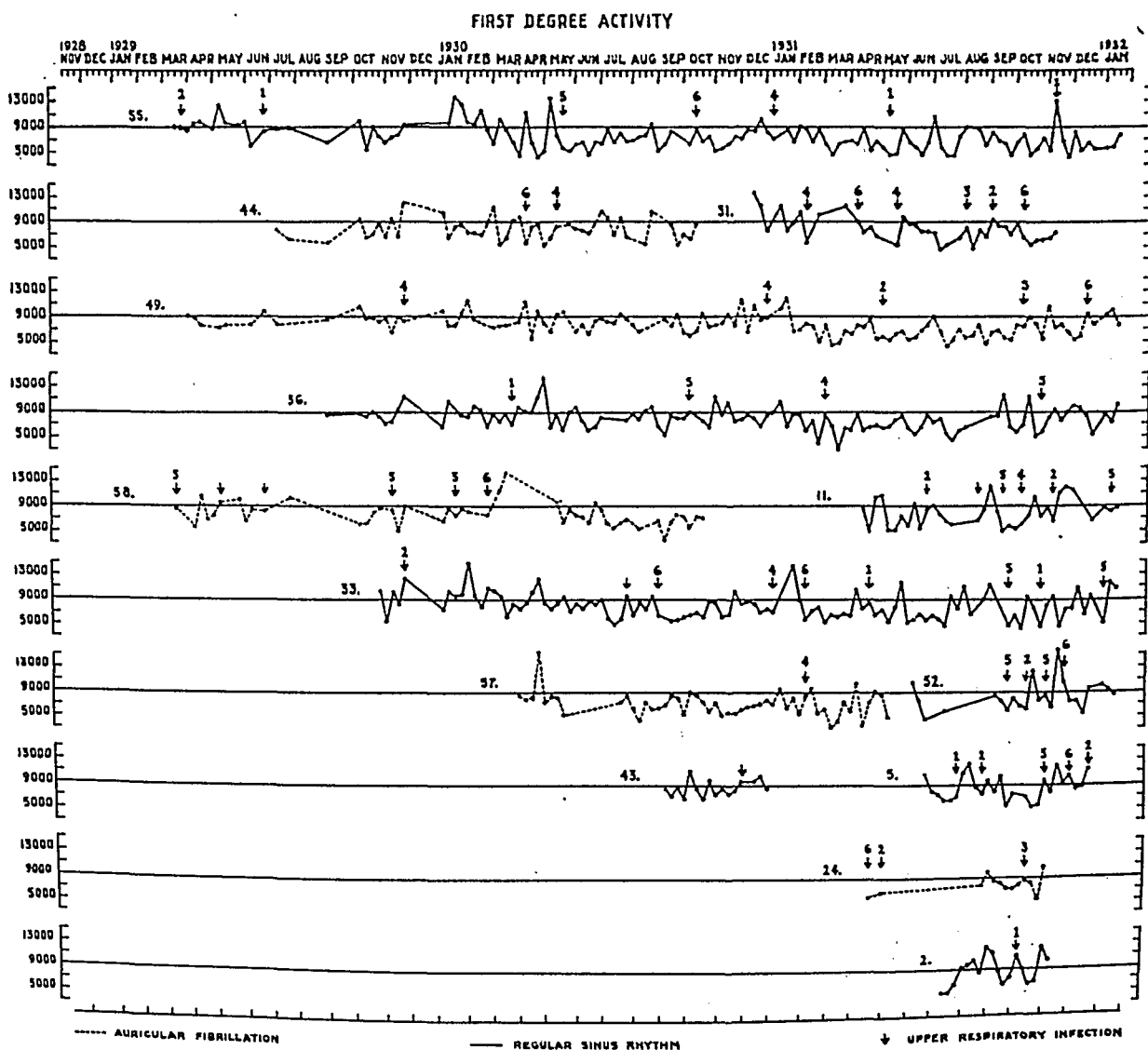


FIG. 3. Arrows designate upper respiratory infections in relation to weekly leukocyte counts. Arrows with numerals above designate upper respiratory infections and the number of days after the weekly leukocyte counts. Numerals at the beginning of each curve designate case numbers.

upper respiratory infections (36 per cent to 78 per cent), with only slight increase of rheumatic activity (66 per cent. to 72 per cent). In addition, the curves showed a seasonal incidence of rheumatic activity in excess of the seasonal incidence of upper respiratory infections, suggesting that rheumatic activity was present during some periods without prior infections. This was particularly apparent during the summer seasons.

A relationship between upper respiratory infections and rheumatic activity was not evident since the seasonal incidence of rheumatic activity did not vary directly with the seasonal incidence of upper respiratory infections.

The Relationship of Upper Respiratory Infections to Leukocytosis. Leukocytosis, often the only evidence of the presence and persistence of

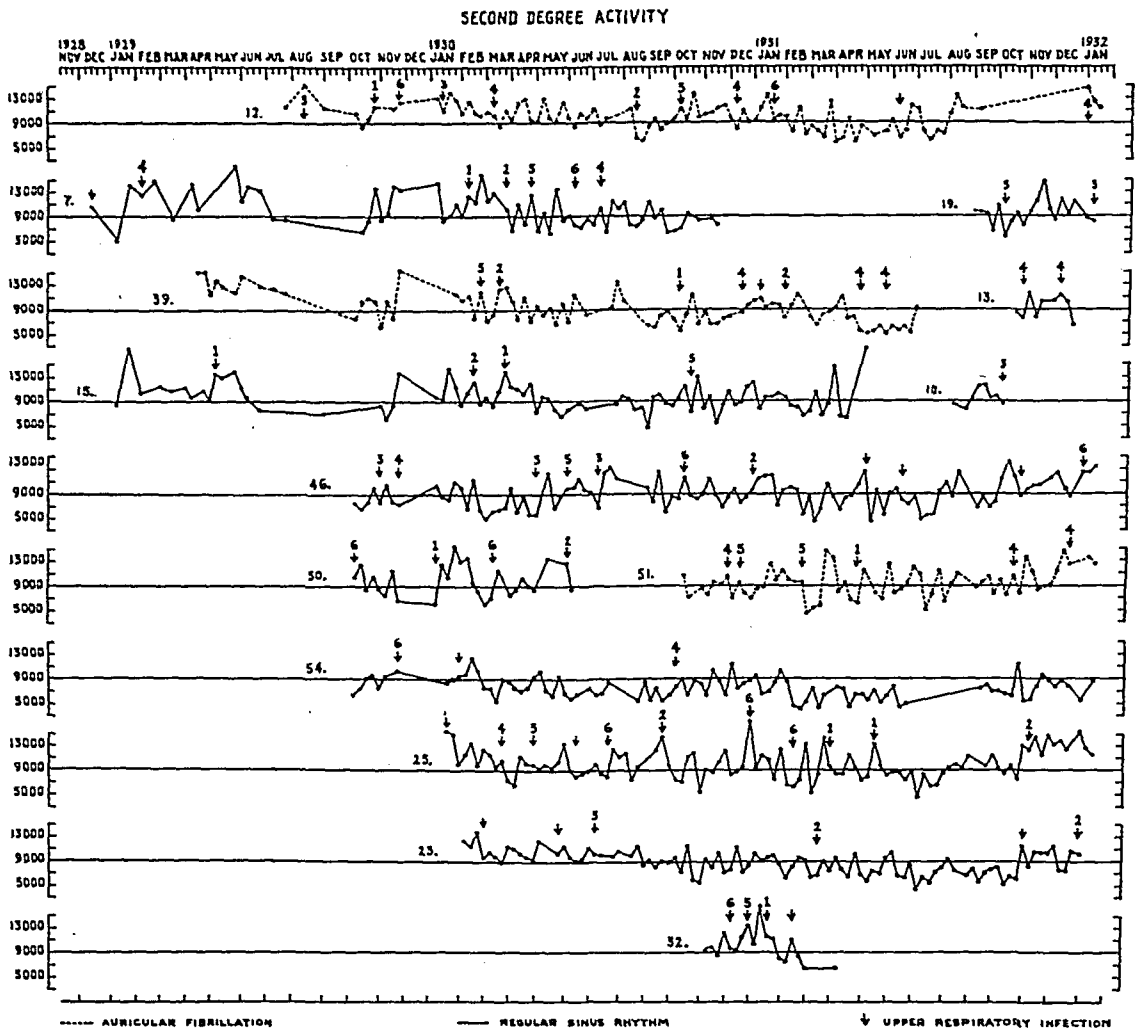


FIG. 4. Arrows designate upper respiratory infections in relation to weekly leukocyte counts. Arrows with numerals above designate upper respiratory infections and the number of days after the weekly leukocyte counts. Numerals at the beginning of each curve designate case numbers.

rheumatic activity,⁴¹ was examined with regard to its relationship to upper respiratory infections. The leukocyte curves of the cases were divided into four groups according to the classification of rheumatic activity (inactive, first, second, and third degrees).⁴² The date of onset of upper respiratory infections was ascertained and recorded in relation to the weekly leukocyte counts.

Inactive (figure 2). Cases considered inactive during the period of observation failed to show leukocytosis prior to or following upper respiratory infections.

First Degree Activity (figure 3). The majority of upper respiratory infections in this group were not followed by leukocytosis. In some instances (Cases 49, 56, 58) leukocytosis was of short duration, whereas in others (Cases 2, 33, 43, 49, 56) it was present prior to the onset of the upper

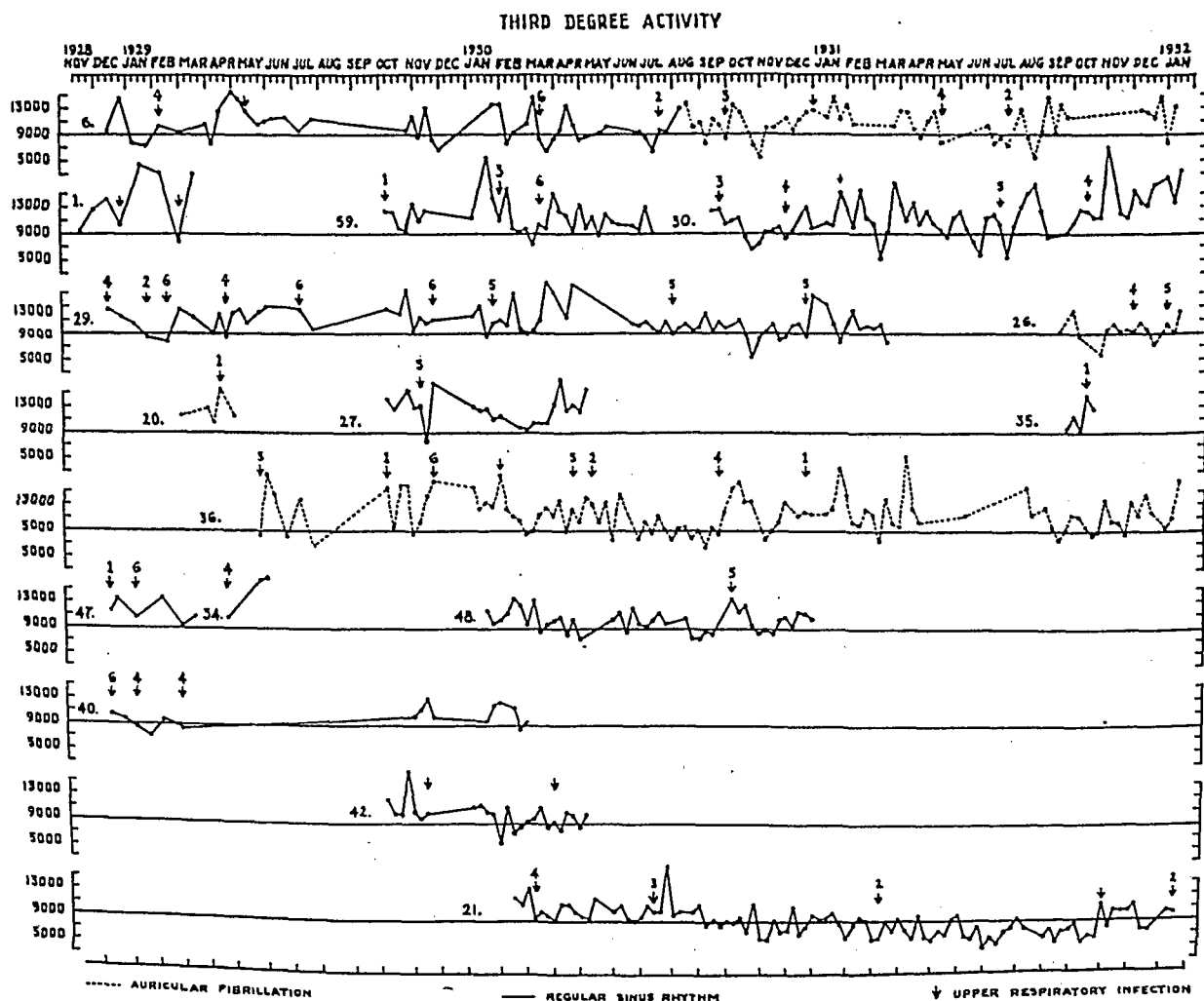


FIG. 5. Arrows designate upper respiratory infections in relation to weekly leukocyte counts. Arrows with numerals above designate upper respiratory infections and the number of days after the weekly leukocyte counts. Numerals at the beginning of each curve designate case numbers.

respiratory infections and became markedly elevated within one to three weeks after the infections (Cases 11, 33, 35, 49, 58). In some instances there was a series of upper respiratory infections associated with leukocytosis (Cases 5, 11, 52).

Second Degree Activity (figure 4) and *Third Degree Activity* (figure 5). Leukocytosis was a more or less constant feature in both groups and was usually present prior to the occurrences of upper respiratory infections.

In many instances leukocytosis was increased following upper respiratory infections, becoming markedly elevated within one to three weeks (Cases 32, 50, 54, second degree, figure 4; and Cases 1, 6, 29, 30, 36, 59, third degree, figure 5). Occasionally when the trend of the curve was downward toward normal, upper respiratory infections did not here influence its direction (Cases 25, 39, second degree, figure 4).

It was evident from these curves that upper respiratory infections were not followed by rheumatic activity in the inactive group, whereas, in first, second and third degrees, when rheumatic activity developed following upper respiratory infections, a preëxisting active process was usually present.

DISCUSSION

It cannot be deduced from these observations that hemolytic streptococcus upper respiratory infections may not be an etiological factor in rheumatic fever; nor can we, on the other hand, disregard the importance of preëxisting subclinical periods of rheumatic activity, even with regard to recurrences following these specific infections. Many of our cases might have been considered inactive during various periods if it were not for the detailed method employed to detect rheumatic activity. A considerable number of the investigators of the etiology of rheumatic fever failed to determine whether or not their cases were active, but considered them inactive because they were symptom free and assumed that rheumatic activity began with the appearance of clinical manifestations of the disease.

Subclinical periods of rheumatic activity are probably much more prevalent than is generally realized. Not only do they exist in those already afflicted with the disease,^{41, 42, 47} but the disease sometimes assumes this form in several sections of the country, being recognized only by the advent of cardiac lesions.^{6, 48, 49, 50, 51, 52, 53, 54, 55} The appearance of clinical manifestations of the disease following operation, pregnancy, scarlet fever and other circumstances previously mentioned may also be explained on this basis; and perhaps subclinical rheumatic activity is the unknown factor mentioned by Coburn and Pauli¹⁰ with regard to recurrences following hemolytic streptococcus upper respiratory infections.

A general idea of the extent of the prevalence of subclinical periods of rheumatic activity may be gleaned by a comparison of the curve of rheumatic activity of this group for the years 1930 and 1931 with that of Wilson et al., whose study covered this period.¹⁴ Both investigations took place in New York City (figure 6). These authors observed 222 children between five and 15 years of age. The criteria of rheumatic activity in their group were clinical rheumatic recurrences such as polyarthritides, nodules, muscle and joint pains and acute carditis, whereas in this group the criterion was the classification based on the leukocyte count.⁴²

The curves of the seasonal incidence of upper respiratory infections were also included to show the remarkable similarity of the seasonal incidence of rheumatic activity and upper respiratory infections of both groups,

particularly after the curve of rheumatic activity of our study had been reduced 60 per cent. Neither group showed a marked sudden rise of rheumatic activity in the winter and spring (figures 1 and 6) but appeared to fluctuate gradually from season to season.

The variation of rheumatic activity did not conform to the seasonal in-

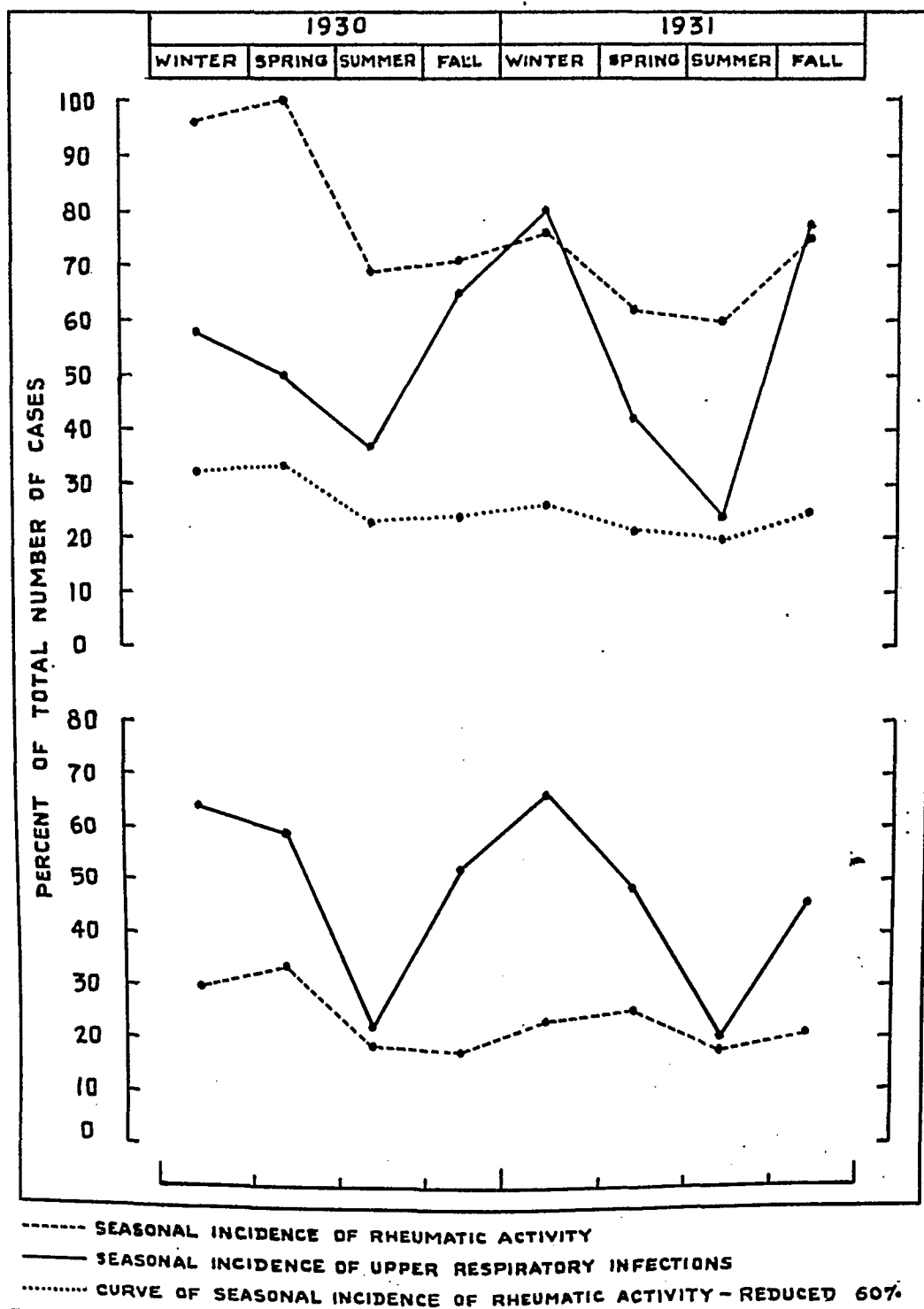


FIG. 6. A comparison of the seasonal incidence of upper respiratory infections and rheumatic activity. Upper group of curves, present study; lower group, that of Wilson et al.¹⁴

cidence of upper respiratory infections but rather to what seemed to be climatic influences. This would account for the lack of a uniform seasonal incidence of recurrences from year to year, since these factors also fluctuate from year to year in the North Temperate Zone. The only constant feature occurred during the summer seasons when rheumatic activity reached its lowest levels. One plausible explanation for the appearance of recurrences because of climatic factors would be complication of a preëxisting active process. Thus, the rheumatic activity in rheumatic cardiac patients who are transferred to warmer climates has a tendency to become quiescent, owing perhaps to milder climatic changes regardless of the incidence of upper respiratory infections.^{43, 44, 50} Another explanation of the disappearance of recurrences would be the absence of hemolytic streptococcus infections, but this would not explain the recrudescences on returning to the Temperate Zone without contracting upper respiratory infections.⁷

The rôle of subclinical rheumatic activity as a phase of the disease has been somewhat underestimated. In this comparative analysis, 60 per cent more rheumatic activity seemed to exist in the subclinical form than was recognized by the clinical manifestations of the disease. This figure may appear high; yet 85 per cent of the cases in this study acquired rheumatic recurrences such as polyarthritides, nodules, acute carditis, muscle and joint pains at some time or other during the course of study,⁴¹ conforming very closely to the pathological evidence of active disease as shown by Rothschild, Kugel and Gross.⁵⁷ These investigators have found active lesions in the myocardium in 80 per cent of the subjects fatally afflicted with rheumatic heart disease in the second and third decades. The absence of clinical manifestations of the disease is not sufficient to consider any case either quiescent or arrested unless carefully observed over an extended period. Subclinical rheumatic activity in rheumatic patients must be thought of in terms of years, not months.⁴¹ Furthermore, if the data herein presented be true, how can there be any degree of certainty that upper respiratory infections preceding initial attacks of rheumatic fever are etiological? The same question can be raised regarding scarlet fever as an etiological factor. Rosenbaum,⁵⁸ studying 1770 cases of scarlet fever, observed 106 cardiac complications. These when broken down gave an incidence of valvular lesions of 1 per cent developing before and during the attack of scarlet fever, which was about the incidence observed in the general school population in New York City.⁵⁹

It is, therefore, apparent that investigations of rheumatic fever based exclusively on clinical manifestations of the disease may be erroneous and misleading.

SUMMARY

1. Eighty-five per cent of the cases of this group experienced a total of 216 upper respiratory infections. The seasonal incidence was similar to that observed in other studies of both rheumatic and non-rheumatic subjects.

2. A direct relationship between the seasonal incidence of upper respiratory infections and rheumatic activity was not evident.

3. The leukocyte curves of the cases were separated into four groups according to the classification of rheumatic activity and studied in relation to upper respiratory infections. In the inactive group upper respiratory infections were not followed by leukocytosis, whereas in cases showing activity of first, second and third degrees, when persistent leukocytosis followed upper respiratory infections, it was usually preceded by leukocytosis of varying periods indicating the existence of preëxisting rheumatic activity.

4. In many instances, particularly in second and third degree activity, leukocytosis became markedly elevated within one to three weeks after the upper respiratory infections, a latent period often mentioned prior to the appearance of recurrences. When this occurred preëxisting rheumatic activity was usually present.

5. Data are offered to suggest that approximately 60 per cent more rheumatic activity exists in the subclinical form than is recognized by clinical manifestations of the disease.

CONCLUSION

In this study evidence is presented to suggest that upper respiratory infections may complicate a preëxisting active rheumatic process rather than initiate it in cases developing rheumatic recurrences following these infections.

REFERENCES

1. BRANSON, W. P. S.: A clinical study on the avenues of rheumatic infection: based upon examination of 75 cases of Sydenham's chorea, *Brit. Med. Jr.*, 1912, ii, 1429.
2. POYNTON, F. J., and PAINE, A.: *Researches on rheumatism*, 1914, Macmillan Co., New York City.
3. McCULLOCH, H., and IRVINE-JONES, E. I. M.: The rôle of infection in rheumatic children, *Am. Jr. Dis. Child.*, 1929, xxxvii, 252.
4. GLOVER, J. A.: Milroy Lectures on the incidence of rheumatic diseases, *Lancet*, 1930, i, 499.
5. COLLIS, W. R. F.: Acute rheumatism and haemolytic streptococci, *Lancet*, 1931, i, 1341.
6. PAUL, J. R.: *The epidemiology of rheumatic fever*, 1930, The Metropolitan Life Insurance Company, New York.
7. COBURN, A. F.: *The factor of infection in the rheumatic state*, 1931, Williams & Wilkins, Baltimore.
8. COBURN, A. F., and PAULI, R. H.: Studies on the relationship of *Streptococcus hemolyticus* to the rheumatic process. 1. Observations on the ecology of hemolytic streptococcus in relation to the epidemiology of rheumatic fever, *Jr. Exper. Med.*, 1932, lvi, 609.
9. COBURN, A. F., and PAULI, R. H.: Studies on the immune response of the rheumatic subject and its relationship to activity of the rheumatic process. IV. Characteristics of strains of hemolytic streptococcus, effective and non-effective in initiating rheumatic activity. V. Active and passive immunization to hemolytic streptococcus in relation to the rheumatic process. VI. The significance of the rise of antistreptolysin level in the development of rheumatic activity. VII. Splenectomy in relation to the development of rheumatic activity, *Jr. Clin. Invest.*, 1935, xiv, 755, 763, 769, 783.
10. COBURN, A. F., and PAULI, R. H.: Studies on the immune response of the rheumatic subject and its relationship to activity of the rheumatic process. I. The determination

- of antistreptolysin titer. II. Observations on an epidemic of influenza followed by hemolytic streptococcus infections in a rheumatic colony. III. Observations on the reactions of a rheumatic group to an epidemic infection with hemolytic streptococcus of a single type, *Jr. Exper. Med.*, 1935, lxii, 129, 137, 159.
11. COBURN, A. F.: Observations on the mechanism of rheumatic fever, *Lancet*, 1936, ii, 1025.
 12. KAISER, A. D.: Influence of the tonsils on rheumatic infection in children, *Jr. Lab. and Clin. Med.*, 1936, xxi, 609.
 13. JONES, T. D., and MOTE, J. R.: The clinical importance of infection of the respiratory tract in rheumatic fever, *Jr. Am. Med. Assoc.*, 1939, cxiii, 898.
 14. WILSON, M. G., WHEELER, G. W., and LEASK, M. M.: The relation of upper respiratory infections to rheumatic fever in children. II. Antihemolysin titres in respiratory infections and their significance in rheumatic fever in children, *Jr. Clin. Invest.*, 1935, xiv, 333.
 15. WILSON, M. G., INGERMAN, E., DuBOIS, R. O., and SPOCK, B.: The relation of upper respiratory infections to rheumatic fever in children. I. The significance of hemolytic streptococci in the pharyngeal flora during respiratory infection, *Jr. Clin. Invest.*, 1935, xiv, 325.
 16. WHEELER, G. W., WILSON, M. G., and LEASK, M. M.: The relation of upper respiratory infections to rheumatic fever in children. III. The seasonal bacterial flora of the throat in rheumatic and non-rheumatic children, *Jr. Clin. Invest.*, 1935, xiv, 345.
 17. WAALER, E.: Development of antifibrinolytic properties in blood of patients with rheumatic fever. Chronic infective arthritis and bacterial endocarditis, *Jr. Clin. Invest.*, 1937, xvi, 145.
 18. NYE, R. N., and WAXELBAUM, E. A.: Streptococci in infectious (atrophic) arthritis and rheumatic fever, *Jr. Exper. Med.*, 1930, lii, 885.
 19. SCHLESINGER, B., SIGNY, A. G., and PAYNE, W. W.: Further studies on the aetiology of acute rheumatism, *Lancet*, 1935, i, 1090.
 20. KEEFER, C. S., and SPINK, W. W.: Studies of hemolytic streptococcal infection. III. The characteristics of the hemolytic streptococci isolated from patients with erysipelas, *Jr. Clin. Invest.*, 1937, xvi, 155.
 21. ARCHER, B. H.: Rheumatic fever. Relationship of preceding infection, tonsillectomy, and mode of onset, *New York State Jr. Med.*, 1938, xxxviii, 1177.
 22. BLAND, E. F., and JONES, T. D.: Clinical observations on the events preceding the appearance of rheumatic fever, *Jr. Clin. Invest.*, 1935, xiv, 633.
 23. BOAS, E. P., and SCHWARTZ, S. P.: Some modes of infection in rheumatic fever, *Am. Heart Jr.*, 1927, ii, 375.
 24. HILLER, R. I., and GRAEF, I.: An epidemic of rheumatism at a cardiac camp, *Am. Heart Jr.*, 1928, iii, 271.
 25. SHAPIRO, M. J.: The natural history of childhood rheumatism in Minnesota, *Jr. Lab. and Clin. Med.*, 1936, xxi, 564.
 26. WEINSTEIN, I., and STYRON, W. C.: Bacteriologic study of throats in rheumatic and non-rheumatic fever, *Arch. Int. Med.*, 1934, liii, 453.
 27. SWIFT, H. F.: The heart in infection, *Am. Heart Jr.*, 1928, iii, 629.
 28. SWIFT, H. F.: The nature of rheumatic fever, *Jr. Lab. and Clin. Med.*, 1936, xxi, 551.
 29. SWIFT, H. F.: Factors favoring the onset and continuation of rheumatic fever, *Am. Heart Jr.*, 1931, vi, 625.
 30. SWIFT, H. F.: Rheumatic fever, *Nelson's Loose Leaf Med.*, 1931, i, 401, Thomas Nelson & Sons, New York.
 31. BUNIM, J. J., and McEWEN, C.: The antistreptolysin titer in rheumatic fever, arthritis and other diseases, *Jr. Clin. Invest.*, 1940, xix, 75.
 32. SWIFT, H. F., DERICK, C. L., and HITCHCOCK, C. H.: Bacterial allergy (hyperergy) to nonhemolytic streptococci in its relation to rheumatic fever, *Jr. Am. Med. Assoc.*, 1928, xc, 906.

33. ZINSSER, H., and YU, H.: The bacteriology of rheumatic fever and the allergic hypothesis, *Arch. Int. Med.*, 1928, xlii, 301.
34. IRVINE-JONES, E. I. M.: Skin sensitivity of rheumatic subjects to streptococcus filtrates. Its relationship to rheumatic fever, *Arch. Int. Med.*, 1928, xlii, 784.
35. POYNTON, F. J., and SCHLESINGER, B.: Recent advances in the study of rheumatism, 1931, P. Blakiston's Son & Co., Philadelphia.
36. SWIFT, H. F.: Rheumatic fever, *Jr. Am. Med. Assoc.*, 1929, xcii, 2071.
37. SWIFT, H. F., DERICK, C. L., and HITCHCOCK, C. H.: Rheumatic fever as a manifestation of hypersensitiveness (allergy or hyperergy) to streptococci, *Trans. Assoc. Am. Phys.*, 1928, xliii, 192.
38. JONES, T. D., and MOTE, J. R.: The phases of foreign protein sensitization in human beings, *New England Jr. Med.*, 1934, ccx, 120.
39. RINEHART, J. F., CONNOR, C. L., and METTIER, S. R.: Further observations on pathologic similarities between experimental scurvy combined with infection, and rheumatic fever, *Jr. Exper. Med.*, 1934, lix, 97.
40. RINEHART, J. F.: An outline of studies relating to vitamin C deficiency in rheumatic fever, *Jr. Lab. and Clin. Med.*, 1936, xxi, 597.
41. JUSTER, I. R.: The significance of rheumatic activity in chronic rheumatic heart disease. Part I. Intensity and extent, *Am. Heart Jr.*, 1938, xv, 1.
42. JUSTER, I. R.: The significance of rheumatic activity in chronic rheumatic heart disease. Part II. A method of classification, *Am. Heart Jr.*, 1939, xvii, 669.
43. TOWNSEND, J. G.: Epidemiological study of the minor respiratory diseases, Reprint No. 966 from United States Public Health Service Reports, 1924, 2669.
44. TOWNSEND, J. G., and SYDENSTRICKER, E.: Epidemiological study of the minor respiratory diseases, Reprint No. 1133, United States Public Health Report, 1927, 99.
45. BOCK, A. V.: Clinical observations, complications, and treatment of acute upper respiratory tract infections, *ANN. INT. MED.*, 1938, xii, 317.
46. KNEELAND, Y., JR., and DAWES, C. F.: Studies on the common cold. V. The relationship of pathogenic bacteria to upper respiratory disease in infants, *Jr. Exper. Med.*, 1932, lv, 735.
47. BLAND, E. F., and JONES, T. D.: The delayed appearance of heart disease after rheumatic fever, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1380.
48. WHITE, P. D., and JONES, T. D.: Heart disease and disorders in New England, *Am. Heart Jr.*, 1928, iii, 302.
49. SAMPSON, J. J., CHRISTIE, A., and GEIGER, J. C.: Incidence and type of heart disease in San Francisco school children, *Am. Heart Jr.*, 1938, xv, 661.
50. VIKO, L. E.: Heart disease in the Rocky Mountain region, *Am. Heart Jr.*, 1930, vi, 264.
51. HART, A. D., JR., WOOD, J. E., JR., and DAUGHTON, A. D.: Rheumatic fever in Piedmont, Virginia. I. Incidence and clinical manifestations, *Am. Jr. Med. Sci.*, 1934, clxxxvii, 352.
52. GEIGER, J. C., SAMPSON, J. J., MILLER, R. C., and GRAY, J. P.: A survey of heart disease morbidity in San Francisco, *Am. Heart Jr.*, 1936, xii, 137.
53. CHRISTIE, A.: Rheumatic fever in northern California, *Am. Heart Jr.*, 1936, xii, 153.
54. BENJAMIN, J. E.: The heart disease situation in Cincinnati, *Am. Heart Jr.*, 1927, ii, 637.
55. LONGCOPE, W. T.: Variations in manifestations of rheumatic fever in relation to climate, *ANN. INT. MED.*, 1931, v, 401.
56. NICHOL, E. S.: Rheumatic heart disease in southern Florida. Incidence and clinical notes, *Am. Heart Jr.*, 1933, ix, 63.
57. ROTHSCILD, M. A., KUGEL, M. A., and GROSS, L.: Incidence and significance of active infection in cases of rheumatic cardiovalvular disease during the various age periods. A clinical and pathological study, *Am. Heart Jr.*, 1934, ix, 586.
58. ROSENBAUM, H. A.: The heart in scarlet fever, *Arch. Int. Med.*, 1920, xxvi, 424.
59. Report of the Committee to Make a Study of Heart Disease in the State of New York: Medical Society of the State of New York, 1928.

PERIARTERITIS NODOSA; REPORT OF FIVE CASES *

By MORRIS M. BANOWITCH, M.D., F.A.C.P., SILIK H. POLAYES, M.D.,
and RICHARD CHARET, M.D., *Brooklyn, New York*

SINCE the first pathological description by von Rokitsansky,¹ and the clinical and pathological correlation by Kussmaul and Maier,² more than 300 cases of periarteritis nodosa (panarteritis nodosa) have been described in the literature. The diagnosis during life has been rarely made, the great majority being discovered at the postmortem table. However, in more recent years the frequency of antemortem diagnoses has increased. We believe that, with proper appreciation of the pathology of the clinical picture, more cases of this affection can be recognized during the lifetime of the individual. We are reporting five cases that occurred in our service at the Cumberland Hospital during the past two years, four of which were diagnosed before the death of the individuals.

CASE REPORTS

Case 1. A. M., aged 25 years, a beautician, was admitted to the Cumberland Hospital on July 18, 1935 with the chief complaint of abdominal pain and fever, both of one month's duration; tingling and numbness of the hands, forearms, and left foot of four days' duration. During the preceding month there were marked eructations of gas, loss of appetite, loss of weight (10 to 15 pounds), chills, and sweats.

The entire symptom-complex commenced six weeks before admission. At the onset, he felt chilly; his temperature was 102° and he sweated. A local physician was called in and made a diagnosis of la grippe. These symptoms persisted for seven days. After this he had a period of well-being that lasted for a week. At this time he developed an attack of hives over the extremities and trunk. This continued for four days and was attributed by his physician to the medication. At this time he began to notice pains in his feet accompanied by swelling and a temperature of 102°. The following day, abdominal cramps developed. These pains in the abdomen were "belt-like" and were almost continuous. The discomfort had no apparent relation to food or to the type of food taken. Accompanying, were daily attacks of vomiting of a watery, colorless to yellowish-green material. No blood was noted. When he did not vomit, gaseous eructations were annoying. Fever varied between 104° and 105°. All these symptoms persisted until four days before admission. At this time, he noted a numbness and tingling of the left hand and forearm up to the elbow, the right hand and lower half of the forearm, and the left foot.

Family History: Essentially negative.

Previous Personal History: Attack of hives at 7 years. Tonsillectomy in childhood. At the age of 10 years, he had a condition which was suspected of being typhoid but no definite diagnosis was made. He never smoked or drank alcoholic beverages, coffee, or tea.

Physical Examination: The patient was a poorly nourished, emaciated, white male, showing evidence of loss of weight and looking acutely ill. He was apprehensive,

* Received for publication November 26, 1940.

From the Medical Service (Dr. H. Joachim, Director) and the Pathology Department, Cumberland Hospital, Brooklyn, N. Y.

spoke incoherently. Skin was hot. Scalp, thinning hair. No tenderness over sinuses elicited; they transilluminated well. Pupils were regular, equal, and reacted to light and accommodation; conjunctivae pale. No petechiae noted. Tongue was dry. No petechiae noted on buccal mucosa. Dullness at base of right lung with diminished breath sounds. Point of maximal intensity of apex impulse in fifth left intercostal space $9\frac{1}{2}$ cm. from midsternal line, soft systolic murmur at base, loudest at pulmonary area. Peripheral vessels appeared fibrotic. Liver and spleen not palpable. There was tenderness over the entire right half of the abdomen. Small, hard, movable lymph glands in both axillae; the right epitrochlear was palpable. No edema of extremities. Dorsalis pedis and posterior tibial arteries were easily palpable. Both forearms were extremely tender, and many purpuric spots noted on volar surfaces. Eyegrounds were essentially normal except for mild anemia of the retina.

Laboratory Studies: Blood Wassermann test negative (on two occasions). Spinal fluid was clear, pressure normal, 18 cells, slight increase in globulin. Wassermann negative. Colloidal gold, 0000000000.

Blood chemistry on admission: Blood sugar 116 mg. per 100 c.c.; urea nitrogen 42.5 mg. per 100 c.c.; creatinine 2.6 mg. per 100 c.c.

Blood chemistry three days before death: Blood sugar 142 mg. per 100 c.c.; urea N 46 mg. per 100 c.c.; creatinine 2.2 mg. per 100 c.c. Icterus index 4.1. Van den Bergh reactions negative. Three blood cultures were sterile. Widal negative. Sputum negative for tubercle bacilli on two occasions. Cultures of urine negative for organisms.

Urine on admission: Specific gravity 1.014. Faint trace of albumin, 30 red blood cells per high power field. Four other specimens of urine showed increasing quantities of albumin, numerous red blood cells, and both hyaline and finely granular casts.

Blood count on admission: white blood cells 27,200, red blood cells 2,640,000, hemoglobin 40 per cent, polymorphonuclear neutrophils 79 per cent, monocytes 3 per cent, lymphocytes 18 per cent, eosinophiles 0.

Red blood cells were normal in size and shape, but showed marked central pallor. White blood cells were all mature. Blood sedimentation time (18 mm.) 10 minutes.

Blood count two days before death: red blood cells 2,840,000, white blood cells 15,100, monocytes 11 per cent, lymphocytes 14 per cent, eosinophiles 0, polymorphonuclear neutrophils 75 per cent.

Blood pressure 140 mm. Hg systolic and 68 mm. diastolic; 132 mm. systolic and 74 mm. diastolic.

Roentgen-ray of the chest showed the heart to be somewhat enlarged to the left with a bulge in the left auricular pulmonic angle. There was no evidence of parenchymal or pleural involvement.

Flat plate of the abdomen showed marked gaseous distention.

Course: During the entire stay of seven days at the hospital, the temperature varied between 101° and 103° ; the pulse was rapid and not proportional to the temperature. On the fifth day after admission, tremor of both hands and legs developed, and the abdominal pain and tenderness persisted. He often complained of blurring of vision and some haziness. Mentally he was dull and had to hesitate and think before understanding questions asked. On the morning of the day of his death (5:00 a.m.), he suddenly became cool and clammy, with cold perspiration, and the tremors of hands and feet increased. Respirations were of the Biot type. Temperature at that time was 101° , pulse 120. He coughed considerably, expectorating blood-tinged sputum. He voided smoky-red urine. This state of affairs persisted until the time of his death.

Necropsy, Case 1. General: The body is that of a well-developed and undernourished young adult white male. The skin is fair, and the hair is straight and dark. There is slight icterus of skin and conjunctivae. A petechial hemorrhage is observed on the conjunctiva of the left lower lid. Purpuric spots are present on the

volar surfaces of both arms. A "splinter" hemorrhage is present under the nail of the left middle finger.

Cavities: Peritoneal cavity contains 350 c.c. of clear yellow fluid. Right pleural cavity contains 200 c.c. of clear yellow fluid. Pericardial fluid is slightly increased in quantity.

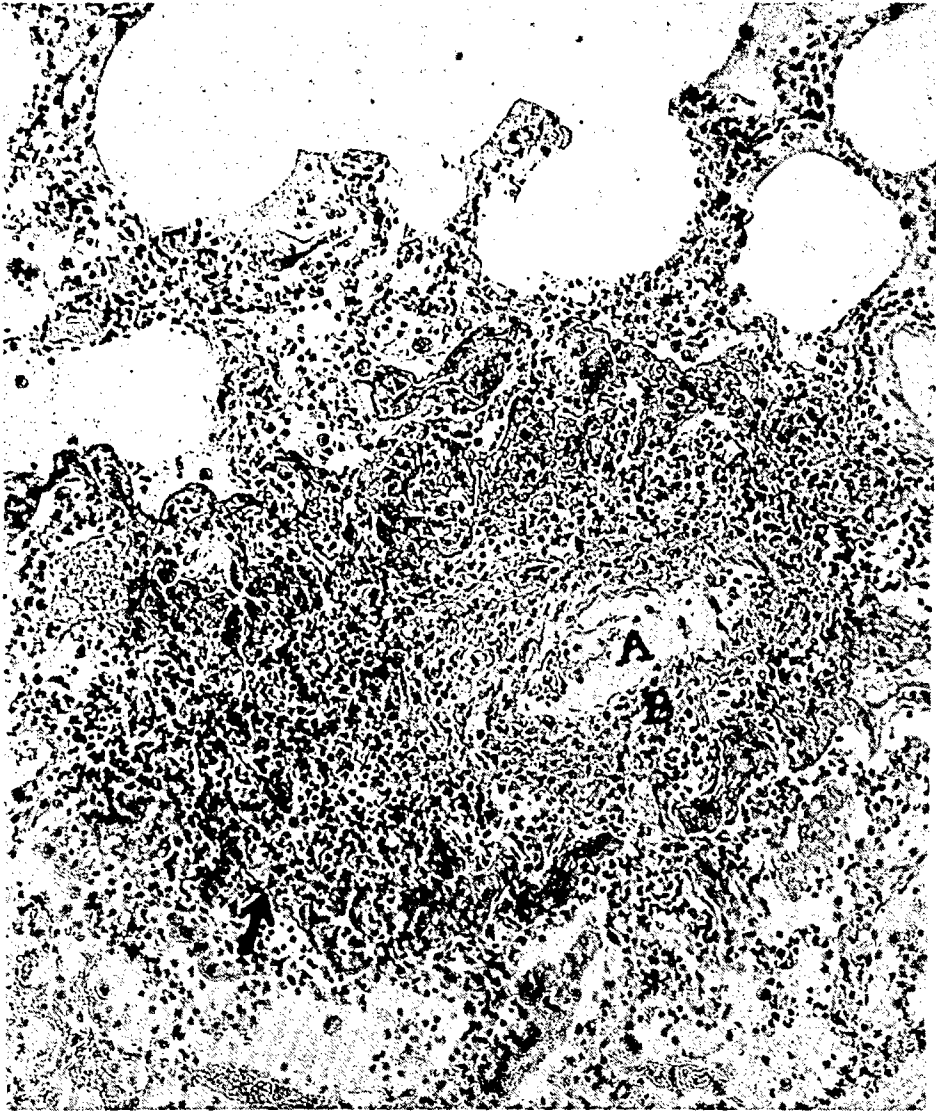


FIG. 1. High power magnification of a characteristic section of lung of case 1. Note small artery (*A*) the wall of which (*B*) is infiltrated with leukocytes, the infiltrate extending into adjacent perivascular structures (arrow).

Cardiovascular system: Heart weighs 390 gm. Some of the epicardial vessels are occluded by thrombi and present nodular thickenings (see visceral arteries). The ventricles are moderately dilated and the myocardium slightly hypertrophied. A sub-endocardial fibrous nodule is found on the atrial surface of the posterior mitral leaflet.

The aorta and other peripheral vessels including veins are in an excellent state of preservation, presenting only a very occasional area of perivascular round cell infiltration of the adventitia.

Visceral arteries of the various organs described below show the following changes occurring either separately or in combination:

- (a) intimal proliferation with or without infiltration of portions or of the entire vessel wall by polynuclear, mononuclear and numerous eosinophilic leukocytes;
- (b) medial necrosis of varying degree;
- (c) aneurysms, single or multiple;
- (d) thrombi occluding vessels;
- (e) recanalization of thrombi;
- (f) fibrous tissue replacement of thrombi.

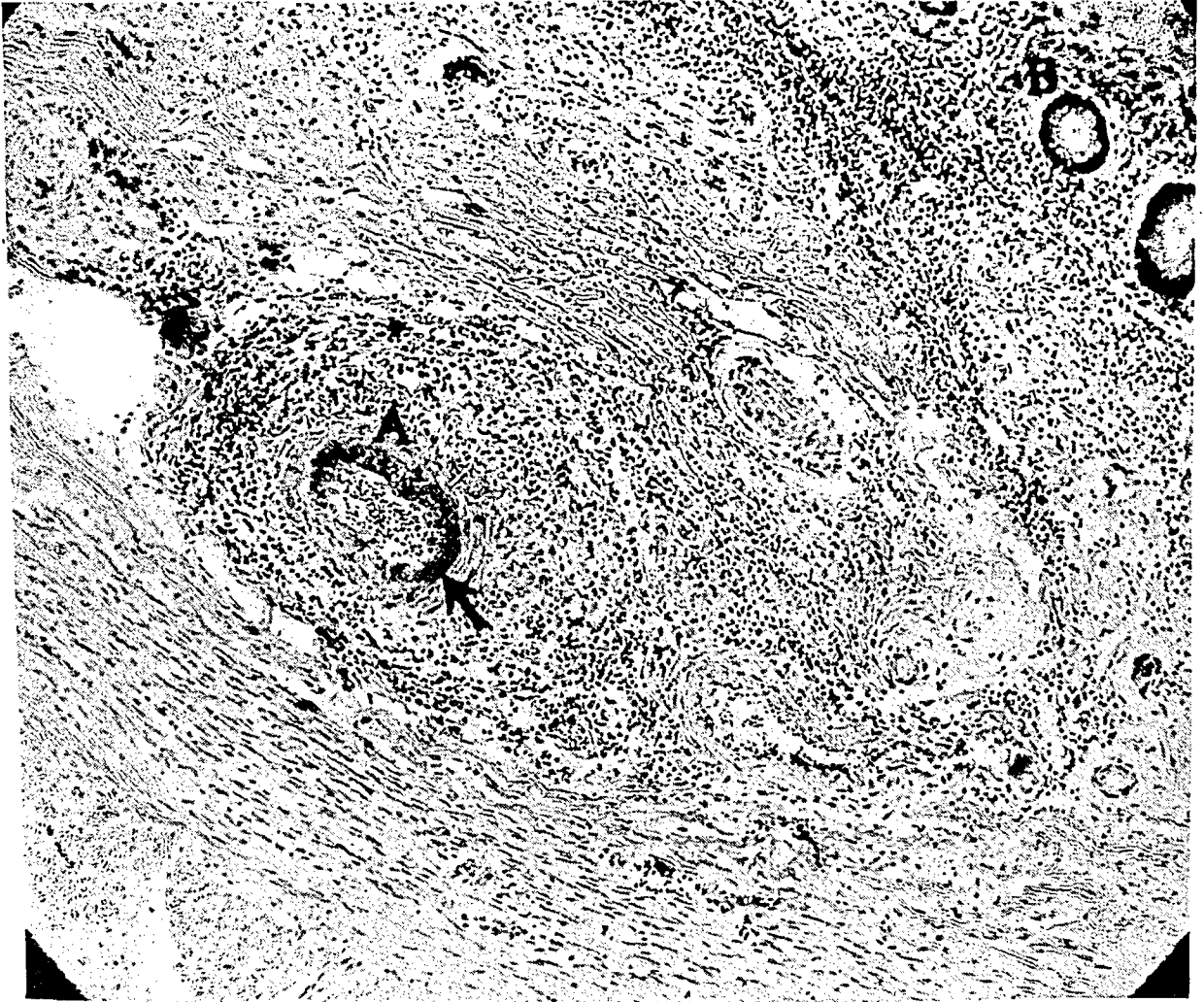


FIG. 1A. Cross section of the appendix of case 1, showing the characteristic and prominent medial necrosis (arrow) as well as acute inflammatory infiltrate in the wall of a small artery (A) in the muscularis. Note the infiltrative process extending into the mucosa (B). (180X).

Respiratory System: The pulmonary arteries are markedly involved in the acute phase of the inflammatory lesions described above (figure 1). Many of the vessels are occluded by thrombi, resulting in hemorrhagic infarctions which extend to the pleural surface. The posterior borders of the lower lobes also contain patchy areas of gray hepatization. Many alveoli are filled with "heart failure" cells.

Gastrointestinal System: Gross lesions are not demonstrable anywhere along the

tract, although microscopically extensive acute arteritic changes are found in the mesenteric vessels which supply their respective segments of gut. In the appendix, the submucosal as well as the serosal vessels show acute arteritis in its exudative form, with pronounced medial necrosis, producing the characteristic picture of the acute phase of the disease (figure 1A).

Biliary system: Liver weighs 1970 gm. Red mottling of hepatic parenchyma is seen through a smooth Glisson's capsule. These areas of discoloration are produced by fresh thrombotic occlusion of branches of the hepatic artery (figure 2). All stages



FIG. 2. Cut surface of liver of case 1, showing thrombus in branches of hepatic artery (A) as well as yellow and red mottling of parenchyma. The arrows point to pyramidal, red and gray peripheral infarcts.

of periarteritis, acute as well as healed, and the changes in the hepatic parenchyma secondary to the vascular lesions are demonstrable in this organ. Most of the liver lobules present periportal infiltration, hemorrhagic extravasation, compression of bile ducts, bile retention, foci of fat replacement, and various degrees of fibrosis.

The gall-bladder is filled with dark fluid bile and the wall is thickened by an acute and subacute periarteritic process. At the tip of the fundus, there is a saccular dilatation of the wall, about 2 cm. in diameter.

Pancreas weighs 120 gm. and presents acute and subacute periarteritis, with but slight parenchymal changes.

Spleen weighs 190 gm. The capsule is smooth and the corpuscles are prominent. Arterial lesions similar to those described in the liver are found in abundance. Many of the central arterioles of follicles show necrosis of their walls. Fibroblasts are seen radiating from the central arteriole and replacing the lymphoid cells of many follicles.

Urinary system: The right kidney weighs 125 gm. and the left 225 gm. Capsules strip with difficulty, exposing numerous yellow, gray and red areas of discoloration due to old anemic and recent hemorrhagic infarcts. The cut surfaces disclose numerous arteries which are filled with thrombi some of which occupy aneurysms, leading to areas of infarction. Microscopically, all stages of periarteritis are demonstrable

although the acute phase is most prominent (figure 2A). Many glomeruli are necrotic or completely replaced by fibrosis and hyalinization. Tubules are distorted, many dilated and filled with hemoglobin, cellular, or hyalin casts. The walls of the ureters present nodular thickenings due to thromboarteritis, in areas producing partial obstruction to the lumen.

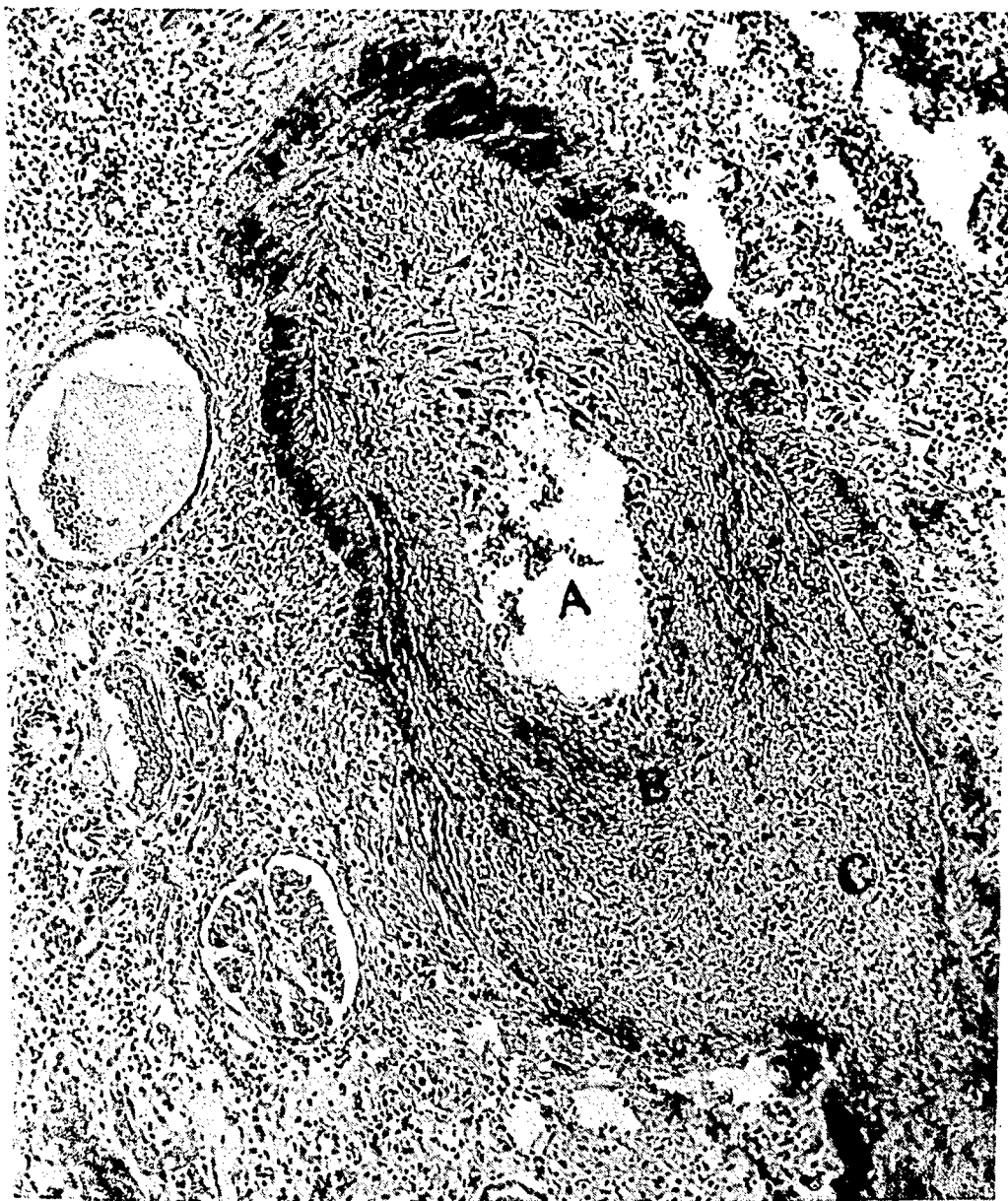


FIG. 2A. Section of kidney of case 1, showing a characteristic acute arteritis. Note narrowed lumen (A), also the infiltrate, edema and medial necrosis (B) of the vessel wall. The polynuclear cell infiltration is most marked in the outer coats (C) of the vessel (60 X).

Endocrine system: Thyroid shows increased colloid secretion. Thymus is absent. Adrenals weigh 15 gm. The periadrenal vessels show acute and subacute arteritis. The vessels of the parenchyma proper show only slight or no involvement. Pituitary shows a comparative increase of chromophile cells.

Lymphatic system: The mesenteric and preaortic nodes show extensive acute periarteritis. The exudative process appears to be most marked in the vessel wall, where aneurysm or branching occurs.

Skeletal system: The orbital muscles of the left eye present a mild periarteritis.

Central nervous system: Brain weighs 1555 gm. Some of the superficial meningeal vessels contain thrombi. The left carotid artery contains a thrombus which extends into the ophthalmic and cerebral branches. The anterior superficial portion of the left frontal lobe presents an area about 2 cm. in diameter, in which are found multiple minute thrombi and petechial hemorrhages. This area merges with an irregular area of softening which extends posteriorly through frontal and parietal lobes of the postcentral gyrus. Microscopically, this area of softening shows white cell thrombi occluding many of the arterioles and disintegrated cerebral tissue which is adjacent to these vessels. The medulla shows dilated Virchow-Robin spaces containing red cells.

Spinal cord shows occasional areas of hemorrhagic extravasation into the Virchow-Robin spaces of the anterior horns.

Anatomical Diagnosis: (1) Panarteritis nodosa; (2) multiple petechial hemorrhages and visceral infarcts; (3) cardiac hypertrophy and dilatation; (4) anasarca; (5) lobular pneumonia; (6) icterus.

Summary, Case 1: Male, perfectly well until seven weeks before death, commenced with chilly sensations, fever, sweats lasting seven days, followed by a period of good health for one week. He then had an attack of urticaria with a recurrence of fever, pain and swelling of the feet, continuous abdominal cramps, and later, numbness and tingling of both upper extremities and left foot. The outstanding findings were fever (101° to 103°), loss of weight, anemia, abdominal tenderness, extreme tenderness of muscles of forearms. The laboratory findings were anemia, hemoglobin 40 per cent, leukocytes varying between 15,000 and 27,000, no eosinophilia, polymorphonuclear neutrophils predominating, 75 to 79 per cent; moderate nitrogen retention, and persistent urinary findings of albumin, numerous red blood cells, hyaline and granular casts.

Autopsy revealed definite changes of periarteritis nodosa involving the vessels of the lungs, mesenteric vessels, appendix, liver, gall-bladder, pancreas, spleen, kidneys, periadrenal vessels, the lymphatic nodes, brain and nervous system.

Case 2. M. R., aged 46, was admitted on December 20, 1935 and died on December 28, 1935.

Chief complaints on admission were precordial pain, shortness of breath, and swelling of both legs of one year's duration. In addition to the above symptoms, she complained of pain in the neck of three weeks' duration. This patient was perfectly well until one year before admission. She began to notice shortness of breath increasing in frequency and severity. In addition, she had severe attacks of nocturnal dyspnea. Associated with these symptoms, she had attacks of palpitation, precordial pain, and swelling of both legs. For the past three or four weeks, she complained of pain in the neck radiating down both arms to the finger tips. The right arm and right lower extremity became weaker rather suddenly one week before admission. During the past year she knew that she had sugar in her urine, and that her blood pressure was elevated. She was not on a restricted diet nor was she receiving any insulin.

Family and personal history were essentially negative. She was never ill except for her present disability. Denied gonorrhea and syphilis. She did not smoke, and partook moderately of alcoholic beverages.

Physical examination: Obese colored female who was dyspneic and orthopneic. Pupils were equal, reacted to light and accommodation, conjunctivae of fair color. No petechiae were noted. Examination of fundus revealed tortuous vessels, but no hemorrhages or exudates. There was no evidence of any cranial nerve palsies. Ears and nose were negative. There were many carious teeth. There was no rigidity of the neck, nor were any enlarged glands noted. Heart showed the point of maximal impulse to be in the sixth left intercostal space within the midclavicular line. Sounds

were of fair quality with regular sinus rhythm. The pulmonary second sound was little louder than the aortic second. No murmurs were heard. Dullness of both lung bases with many fine moist râles. Liver enlarged to four fingers below the costal margin. Spleen was not palpable. There was a hard immovable mass that extended from two fingers below the umbilicus into the pelvis. Pelvic examination revealed this mass to be connected with the uterus (fibroid). Sacral edema was present. Both lower extremities were edematous. The right upper and lower extremities showed definite impairment of motor function and diminished reflexes. Rectal examination showed nothing of importance.

Laboratory studies: Blood Wassermann test negative. Urine revealed glucose 2 per cent, no acetone, specific gravity 1.020, no albumin, no casts, several red blood cells per field.

Blood examination: White blood cells 9,200, red blood cells 4,300,000, polynuclears 72, lymphocytes 28, hemoglobin 85 per cent.

Chemical examination of the blood on December 23 showed: Sugar 350.8 mg. per 100 c.c., urea nitrogen 25.8 mg. per 100 c.c., creatinine 1.7 mg. per 100 c.c., uric acid 4.4 mg. per 100 c.c., cholesterol 245 mg. per 100 c.c., cholesterol esters 47 mg. per 100 c.c. On December 26, examination showed: Sugar 339 mg. per 100 c.c., urea nitrogen 38.4 mg. per 100 c.c., creatinine 1.5 mg. per 100 c.c., uric acid 5.3 mg. per 100 c.c.

Clinical course: During her stay at the hospital, her pulse was relatively rapid in relation to the temperature curve, the pulse varying between 100 and 130, the temperature between 99° and 102°. Her blood pressure, 190 mm. Hg systolic and 100 mm. diastolic on admission, varied between 190 and 240 systolic, and 100 and 112 diastolic. In spite of the therapy, the patient continued in congestive heart failure, becoming irrational the day before death. At this time there was considerable drooping of the right side of the mouth, and the tongue deviated to the right. There was complete paralysis of the right lower extremity and marked weakness of the right upper. There was no change in the cardiac findings. There was an increase of râles in both bases of the lungs. The next day the patient died.

Necropsy, Case 2. General: The body is that of a well developed and well nourished negress.

Cavities: Pleural cavities contain numerous fresh adhesions.

Cardiovascular system: Heart weighs 490 gm. The right atrium and ventricle are dilated and the left ventricle is slightly hypertrophied. The coronary arteries show moderate sclerosis and the myocardium presents considerable fibrosis. The mitral valve shows fibrosis of its free margin.

Respiratory system: The trachea and bronchi are congested. The lungs show a healed tuberculous lesion in the left apex and hypostatic congestion with irregularly distributed areas of emphysema in the rest of the parenchyma.

Gastrointestinal system: The entire tract shows congestion of the lining. Pancreas weighs 75 gm. and shows a moderate amount of fibrosis. Spleen weighs 120 gm. and also shows a moderate amount of fibrosis.

Biliary system: Liver weighs 1700 gm. and shows considerable cloudy swelling. The periportal tissues are infiltrated with polynuclear and lymphoid cells.

Gall-bladder contains viscid bile. Its wall is thickened by congestion and infiltration with polynuclear and round cells. The arteries present characteristic medial necrosis with peri-, as well as panarteritis (figure 2B).

Kidneys: The capsules strip with difficulty revealing occasional cortical cysts. The glomeruli and arterioles of the cortex show the characteristic changes of accelerated arteriolosclerosis. Many of the glomeruli are completely hyalinized and many of the arterioles show almost complete obliteration of lumina by the intimal proliferation. Arcuate arteries, and occasionally those of lesser as well as smaller

caliber show medial necrosis and infiltration characteristic of periarteritis nodosa (figure 2C). The calices and rest of the pelvis are markedly dilated.

Ureters are distended due to uterine fibroids which impinge upon the ureteral entrance into the bladder. The wall of the right ureter also presents characteristic periarteritis.

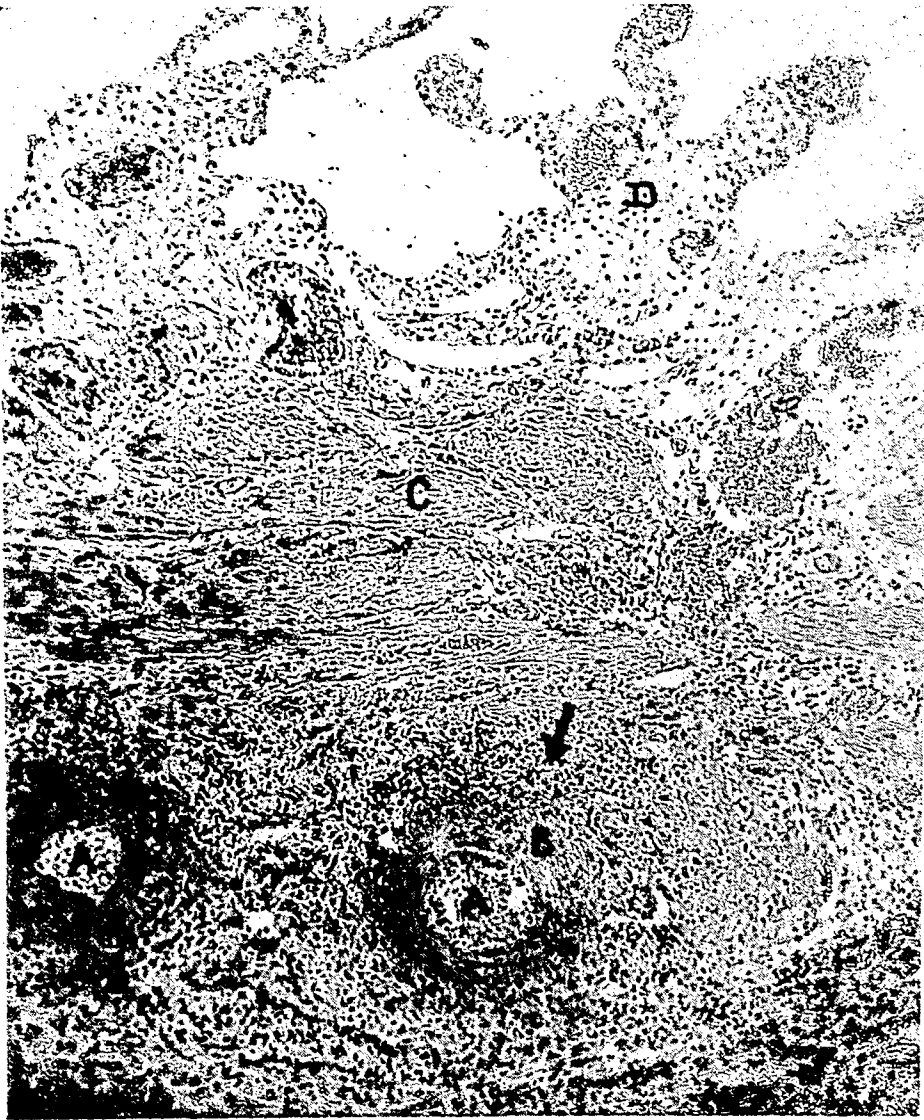


FIG. 2B. High power magnification of gall-bladder of case 2 showing two muscular branches of the cystic artery on cross section (A). Note the medial necrosis (B) and intense polynuclear and eosinophilic infiltrate in adventitia and adjacent perivascular tissue (arrows).

Uterus contains multiple intramural and one large subserous fibroid which distort the organ and press upon the bladder and ureters.

Ovaries are sclerotic and atrophied.

Endocrine system: Adrenals show considerable hemorrhagic extravasation into the parenchyma.

Anatomical diagnosis: (1) Nephrosclerosis (accelerated); (2) panarteritis nodosa; (3) cardiac hypertrophy and dilatation; (4) chronic passive congestion of viscera; (5) fibromyomata uteri (with ureteral obstruction); (6) hydroureter and hydro-nephrosis.

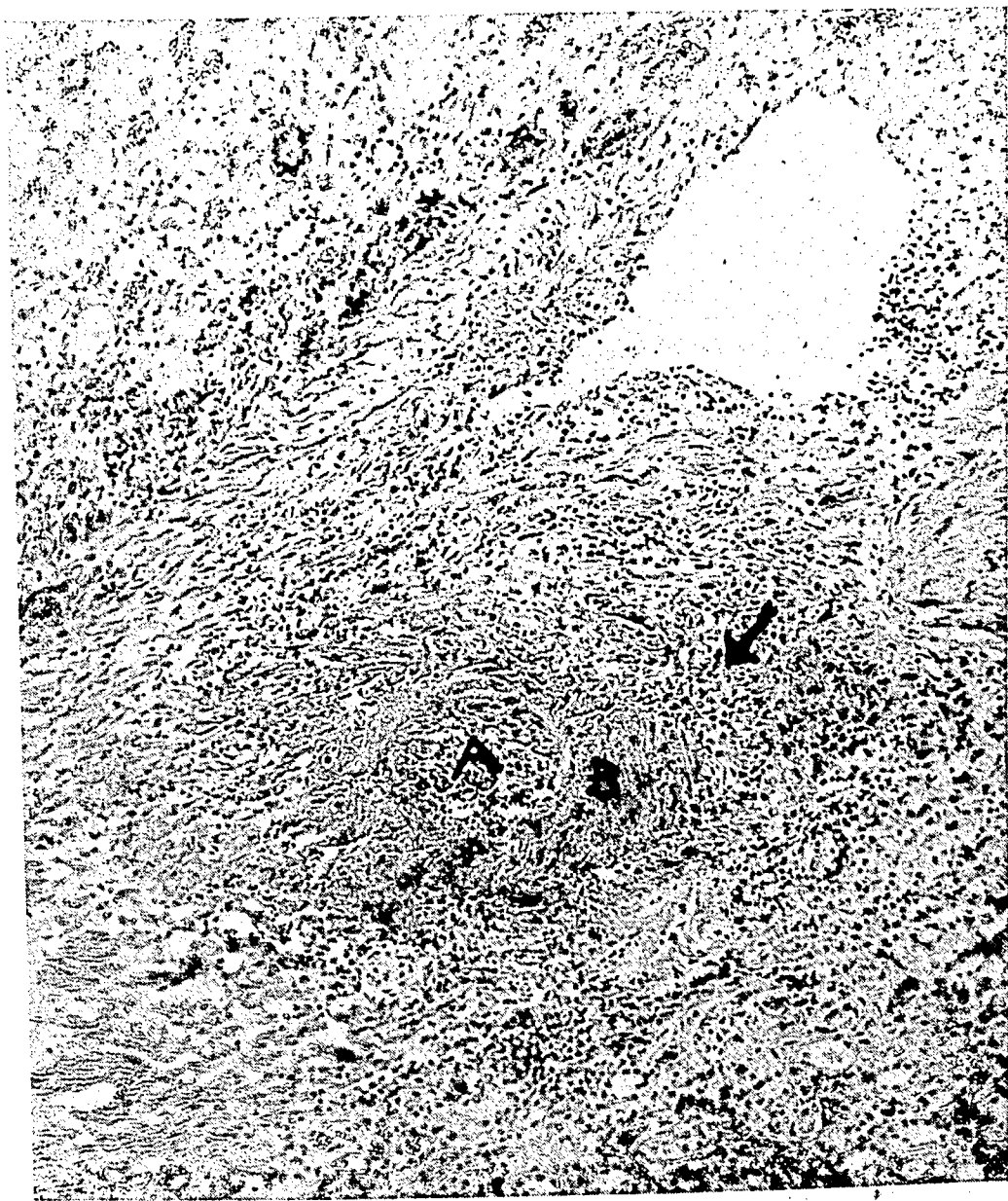


FIG. 2C. High power magnification of a representative portion of kidney of case 2, showing a small artery (A) with the characteristic necrosis of its medial wall (B) and acute inflammatory infiltrate in and about the wall of the vessel (arrow).

Summary, Case 2: This patient was a known diabetic with hypertension. There was gradual progressive heart failure with anginal symptoms of one year's duration. The physical findings were all in agreement with progressive heart failure: orthopnea, large heart, basal râles, large liver, sacral and leg edema. At the end, she developed a right hemiplegia. Laboratory examinations revealed glycosuria, a few red blood cells in the urine; hyperglycemia, 339 and 350 mg. per cent; hemoglobin 85 per cent, white blood cells 9,200.

Autopsy revealed panarteritic changes in the arteries of the gall-bladder and kidneys (permission for opening the cranial cavity was not obtained). The diagnosis of panarteritis nodosa was not made until after the postmortem microscopic study.

Case 3. F. A., aged 55, Italian butcher, was admitted to the service of Dr. J. J. Guttman at Cumberland Hospital on November 9, 1936 and died on April 18, 1937. Chief complaints on admission were chills, fever, and pain in both legs of 11 days' duration. Eleven days before admission he had a sudden chill followed by fever, and after the first chill he had three more at irregular intervals.

Two days after the initial chill, pain and weakness of both legs appeared and were of such severity that he had to remain in bed. However, on close questioning the patient admitted having had a sore throat two weeks prior to the onset of the above symptoms.

Family history showed nothing of importance. He was a moderate drinker and commenced to smoke three years previously. Nine years previously, he was in bed with thrombophlebitis involving both lower extremities. At the age of 17, he contracted malaria in Italy, was treated with quinine, completely cured, and has had no recurrence since.

Physical examination: White, well-nourished male, perspiring profusely, appeared quite ill. The right pupil was irregular and smaller than the left, but both reacted to light and accommodation. No conjunctival petechiae were noted. Many carious teeth were present. Tongue was coated and pharynx quite injected. Chest was emphysematous in shape with inconstant moist râles at the bases of both lungs. The point of maximal impulse of the heart could not be made out. The borders could not be definitely made out. The sounds were regular and of good quality. There were no murmurs. The aortic second sound was louder than the pulmonic second sound. The liver and spleen were not palpable. However, marked tenderness was elicited over the right lower costal margins anteriorly and posteriorly. There was no edema of the extremities nor was there any tenderness in the calf muscles. Complete neurological examination revealed nothing of note. The left epididymis was tender, painful, and definitely thickened.

Laboratory studies: Urine showed albumin 1 to 2 plus with finely granular casts during his entire stay. When jaundice appeared, bile was present. Examination of the urine for arsenic, lead, leucine and tyrosine crystals, and tubercle bacilli was negative. Blood Wassermann was 2 plus on admission, but subsequently repeated Wassermann tests, as well as the provocative test, were negative. Spinal fluid Wassermann was negative. Colloidal gold curve 1122110000. Gonococcus complement fixation was negative. Repeated blood cultures (five) were negative. Agglutination tests for typhoid, paratyphoid, undulant fever, supestifer, and tularemia were negative. Stools were consistently negative for ova, parasites, and *B. typhosus*. Mantoux test was negative. Sputum was negative for tubercle bacilli and spirochetes.

Chemical examination of the blood: Sugar 125 mg. per 100 c.c., urea nitrogen 24 mg. per 100 c.c., creatinine 1.7 mg. per 100 c.c., cholesterol 180 mg. per 100 c.c., cholesterol esters 40 mg. per 100 c.c., icterus index 9.3. *March 19.* Regular sinus rhythm, rate 110. QRS_{1,2,3} slurred; QRS₃ inverted, low voltage. T₁ diphasic, T₂ depressed.

Roentgen-ray of chest: November 10 and 14, December 17, and February 17 negative. March 18: Heart is aortic in configuration, cardio-thoracic ratio 50. An axillary band of density with a more or less sharply defined inner border extends from the base of the right lung field toward the sixth intercostal space posteriorly. The right diaphragmatic leaf is visualized disappearing within the opacity which obscures the base. There is a thickening of the interlobar fissure between the right upper and middle lobes. There is a very marked accentuation of the pulmonary striation, which would indicate the presence of an engorgement of the lesser circulation. The axillary

band of density on the right side is indicative of the presence of fluid in the pleural cavity of the right hemithorax.

Flat plate of abdomen: November 10 negative. November 14: The right ilio-psoas shadow is indistinctly visualized. The left is not visualized at all. Both kidneys are very indistinctly outlined. The lower pole of both kidneys is approximately at the level of the transverse processes of the third lumbar vertebra. Evidence of osteoarthrosis in the form of lipping is noted at the upper and lower articular surfaces of the third lumbar vertebra.

Kidney function tests: specific gravity varied between 1.005 and 1.012, phenol-sulphonphthalein excretion 27.5 per cent in two hours. Bromsulphalein and galactose tolerance tests revealed normal liver function. The congo red test was normal. Sedimentation time varied between 18 and 37 minutes.

Blood examination:

	11/9	11/20	12/5	12/27	1/11	2/3	2/16	3/17
White blood cells	14,650	12,000	7,100	6,800	6,200	4,200	3,900	7,250
Red blood cells, millions	4.8	5	4.22	3.4	3.8	2.6	2.75	3.18
Hemoglobin, per cent	115	85	62	56	65	60	55	52
Polynuclear neutrophiles	86	83	74	70	71	74	80	71
Lymphocytes	14	12	26	30	18	26	18	14
Monocytes		5			4		2	7
Basophiles					1			2
Eosinophiles					4			6
Turck cells					2			

Fragility test of red blood cells normal.

Smear for malaria negative.

Electrocardiograms: *November 21*. Sinus rhythm with pulsus trigeminus. QRS_2 inverted. Premature contractions from right ventricle, one interpolated beat from left ventricle. T_1 isoelectric; T_2 inverted. *January 8*. Regular sinus rhythm, rate 140. P_2 isoelectric. QRS_2 inverted. T_1 inverted; T_2 diphasic.

Intravenous pyelogram: (January 22) Both ilio-psoas muscles are sharply outlined on all the exposures. The kidney shadows are visualized on all the exposures. The left kidney takes the dye better than the right one, and has a bifid pelvis. The right kidney pelvis cannot be made out because of poor concentration of the dye. Neither of the calyces on the left or right side is well visualized and no statement can be made as to the presence of any blunting of the lesser calyces. The right ureter shows a spindle-shaped dilatation about 2 cm. above the ureteropelvic junction. This is visualized on all the exposures.

Roentgen-ray of the left forearm and right leg showed no radiographic evidence of sclerotic changes in the vessels.

Clinical course: The temperature of the first week varied between 103° and 104°; for the next five weeks, 101° and 102°; and the rest of the stay between 99° and 101°, except for the last five days, when it reached subnormal on numerous occasions. The pulse varied between 80 and 120 until three weeks before the end. At this time there were periods when it averaged 130. The blood pressure was 106 systolic and 68 diastolic on admission, continued at this level until the end of the seventh week when it rose to 154 systolic and 100 diastolic, and remained elevated until death. On November 13, he developed transient icteric sclerae associated with epigastric pain and tenderness which disappeared in a few days. On November 21, the pulse became irregular, heart sounds poor, and electrocardiogram showed pulsus trigeminus. On November 25, the extremities became weak and the patient showed positive left Babinski, Oppenheim and Gordon reflexes. On December 7, the spleen was felt. On December 16, position and vibration sense was lost and knee jerks were absent. On January 6, 1937, he developed paroxysmal dyspnea. On January 9, bilateral foot drop appeared. On February 10, the liver was palpable. Both liver and spleen became

progressively larger. On February 16, purpuric spots developed over the legs and gradually disappeared in a few weeks. Weakness became progressively worse. There was progressive atrophy of the muscles, particularly of the extremities, with trophic changes of the hands, arms, and soles of the feet. The patient lost 50 pounds during his stay at the hospital. Signs of heart failure appeared. Patient became irrational and died one week later.

Necropsy, Case 3. General: The body is that of a well developed and fairly nourished white male about 55 years of age.

Cavities: The right pleural space is obliterated by adhesions and enclosed collections of serous fluid. The left contains air and about 1200 c.c. of fluid and clotted blood.

Cardiovascular system: Heart weighs 475 gm. The apex is rounded. The epicardium and endocardium are normal. The myocardium is thickened, and on section shows pale gray streaks. Microscopic examination reveals fibrous replacement, interstitial edema, and cloudy swelling of the muscle fibers. The mitral valve shows fibrous thickening along the closing margin. There is no other more definite pathologic evidence of recent or old rheumatic involvement.

Respiratory system: Trachea and bronchi show an intense acute inflammatory process in the mucosa. The right middle and lower lobes of the lung show a marked broncho-pneumonic process with suppurative bronchiolitis. The left lower lobe is the seat of recent hemorrhagic infarction. Some of the arterioles show inflammatory changes in their walls.

Digestive system: Esophagus shows marked changes in the serosal arterioles, characterized by medial degeneration, partial occlusion of the lumina by thrombi, aneurysmal dilatation and cellular infiltration of the walls.

Small and large intestines show marked submucosal congestion. The splenic flexure of the colon contains submucosal venous thrombi and small diverticula. One section of colon shows metaplasia of lining from columnar to squamous cells.

Spleen weighs 360 gm. and shows congestion.

Pancreas weighs 90 gm. One section shows a small artery the wall of which is the seat of necrosis (especially of the medial coat) with polynuclear leukocytic infiltration. There are many vessels showing aneurysmal dilatation. Some also show fibrosed, hyalinized or recanalized thrombi. These stigmata of healed panarteritis are present throughout.

Biliary system: Liver weighs 1325 gm. The capsular surface is partly nodular and shows depressed scars, hemorrhagic zones and dilated spaces which, on section, are found to be filled with blood and bile. Microscopic examination reveals loss of normal architecture and cirrhosis. Many of the ducts are dilated and filled with bile. The vascular changes are similar to those described in the pancreas. Recent hemorrhagic infarctions are present in abundance.

Gall-bladder and cystic duct are normal.

Common bile duct, its tributaries and ampulla of Vater are all dilated.

Urinary system: The right kidney weighs 100 gm. and the left 160 gm. The cut surface reveals many areas of recent and old infarction (figure 3). Microscopic examination shows advanced changes involving the arteries and arterioles. These changes consist of aneurysmal dilatation or obliteration of the lumina by organized, hyalinized or recanalized thrombi. Various degrees of glomerular and interstitial fibrosis are also present.

Reproductive system: The left testis is atrophied and the epididymis is thickened (figure 3). The vessels in the thickened tunica albuginea show arteritic changes similar to those described in the other viscera. The parenchyma of the gland contains rests of chromaffin cells.

Prostate shows a glandular hyperplasia and an increase in the fibrous stroma. The vascular changes are similar to those observed in the other organs.

Skeletal system: The intercostal muscles are opaque, pale gray in color and microscopically show Zenker's degeneration.

Anatomical diagnosis: (1) Panarteritis nodosa; (2) multiple visceral infarction (renal, pulmonary, hepatic); (3) cirrhosis of liver (atypical, periportal); (4) biliary obstruction (intrahepatic); (5) splenomegaly; (6) myofibrosis cordis; (7) cardiac hypertrophy and dilatation; (8) bronchopneumonia (terminal); (9) hemo-pneumothorax; (10) atrophy and chromaffin rests of testis; (11) metaplasia of intestinal mucosa; (12) pleural adhesions (fibrous); (13) diverticulosis coli; (14) accessory spleen.

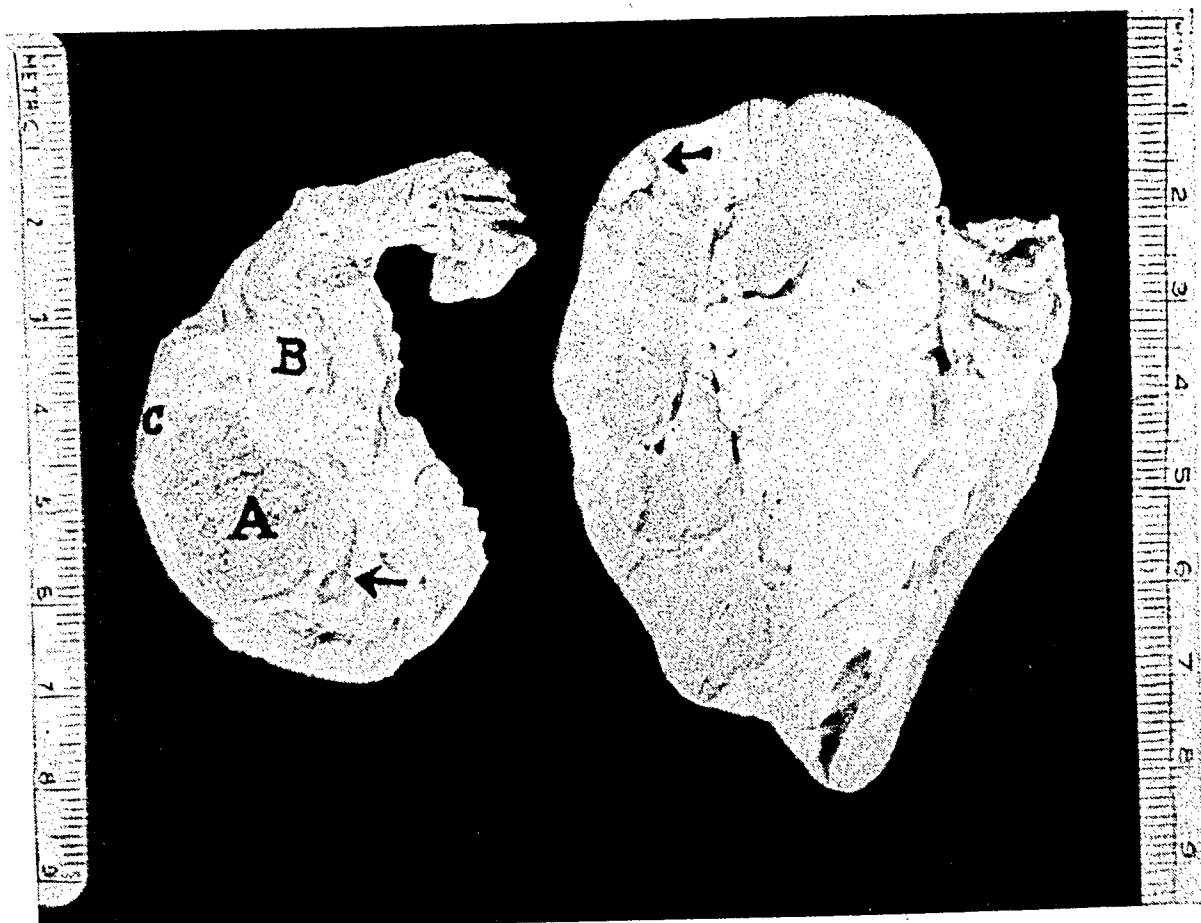


FIG. 3. Cut surfaces of kidney and testis of case 3. Arrows point to infarcts in both organs.

The testis (A) is partly atrophic and the epididymis (B), as well as the tunica albuginea (C) is markedly thickened by fibrous tissue.

Summary, Case 3: Adult male, 55 years of age, was admitted to the hospital with a history of chills, fever, and pain in the legs of 11 days' duration, all following a sore throat two weeks previously.

Repeated examinations during his five months' stay at the hospital revealed a well-nourished male with progressive cachexia, cardiac irregularities and weakness, transient epigastric tenderness, hepatic and splenic enlargement, bilateral foot drop, atrophy of the muscles, particularly of the extremities, purpuric spots over the legs, atrophic changes of the hands, arms, and soles of the feet, transient icterus, and neurological abnormalities. Fever, anemia, and hypertension were present. There was moderate nitrogen retention in the blood with persistent albumin and casts in the urine.

Autopsy revealed characteristic changes of panarteritis nodosa involving the vessels of the lungs, esophagus, intestines, pancreas, liver, kidneys, testes, and prostate.

Case 4. R. T., aged 29, chauffeur, born in British West Indies, admitted to Medical Service, Cumberland Hospital, April 29, 1937, died June 11, 1937.

Chief complaint on admission was pain in legs. Three and a half months before admission, he had sore throat lasting three days; two weeks later, he noticed that he was feverish and began to complain of pain in calves of both legs, especially in the region of the tendo-achilles. This pain persisted and became very intense three weeks before admission. Lying in bed relieved this pain to some extent, but standing or letting the feet hang over the bed aggravated the pain. Three days before admission, he began to notice some pain in the left wrist. There was no redness or swelling of the extremities. Marked anorexia had been present for the past three months. About five months prior to admission, the patient had a toothache followed by swelling and spontaneous rupture through the left lower cheek forming a draining sinus that persisted.

Examination of his past showed that he had measles and mumps as a child. Malaria was present at the age of 14 years, and he recovered promptly under treatment. There was no recurrence. In 1928, he had a urethral discharge lasting two days. Syphilis was denied by name or symptoms. He was a moderate drinker, and since childhood had an unusual craving for salt.

Physical examination: The patient was poorly nourished, pale, apprehensive, and looked acutely ill. Pupils were equal, regular, and reacted to light and accommodation. No nystagmus. No conjunctival petechiae. Tongue coated; pharynx congested; tonsils enlarged and reddened. On the lower left cheek opposite the first molar was a draining apical abscess. Neck showed no rigidity. Lungs were essentially normal. Heart was not enlarged. No murmurs at apex or base. Sounds were regular and of good quality. Liver and spleen were not felt and no tenderness was elicited. There was marked bilateral gastrocnemius tenderness, more marked on the left. Dorsiflexion of both feet induced pain in the calf muscles. There was hyperreflexia in both upper and lower extremities. Babinski negative. No sensory disturbances. Some weakness of both lower extremities. There was no evidence of any cranial nerve involvement. Rectal examination was negative. Eyegrounds revealed mild vascular sclerosis, but no nodules, aneurysms, or dilatation.

Laboratory studies: Repeated urine analyses revealed traces of albumin, red blood cells, white blood cells, and hyaline and granular casts. Specific gravity varied between 1.018 and 1.022. Phenolsulphonaphthalein 65 per cent in two hours.

Blood chemistry, *April 30*: Sugar, 95.2 mg. per 100 c.c., urea nitrogen 14.8 mg. per 100 c.c. *May 27*: Sugar 88.9 mg. per 100 c.c., urea nitrogen 10.9 mg. per 100 c.c. *June 7* (four days before death): Sugar 117.6 mg. per 100 c.c., urea nitrogen 45.4 mg. per 100 c.c., creatinine 3.3 mg. per 100 c.c.; blood chlorides 465 mg. per 100 c.c.; cholesterol 124.3 mg. per 100 c.c.; urea clearance 117.9 per cent (May 14).

Blood Wassermann test negative. Gonococcus complement fixation test negative. Spinal fluid pressure 10 mm. Hg, clear, 8 cells. Wassermann test negative. Colloidal gold 0000000000. Stools persistently negative for ova, blood, and parasites. Stools, urine, and sputum negative for tubercle bacilli. Blood counts:

	May 1	May 7	May 11	May 25	June 2
White blood cells	14,200	19,200	28,800	23,200	22,400
Red blood cells, millions	3.68		3.18	2.9	2.6
Hemoglobin, per cent	75		62	48	40
Polymorphonuclear neutrophiles	79	76	85	78	89
Monocytes	3	11	1	1	2
Lymphocytes	18	4	10	15	8
Eosinophiles	0	7	4	6	1
Basophiles	0	2	0	0	0

Sedimentation time (18 mm.):

Date	Apr. 30	May 11	May 12	May 13	May 14	May 15
Time (in minutes)	8	15	15	12	12	8
Date	May 21	May 31	June 1	June 3	June 8	
Time (in minutes)	9	12	10	6	19	

Mantoux test, 1/1000 mg., negative. Culture from discharging sinus on face showed *Staphylococcus albus*.

Electrocardiograms: *April 30*: T_{1,2} depressed; T₃ isoelectric; T₄ diphasic. *May 13*: T₃ depressed; T₄ diphasic. *May 24*: QRS_{1,2,3} slurred. T_{1,2} depressed; T₄ diphasic. *June 5*: P₃ notched. QRS_{1,2,3} slurred. T₁ isoelectric; T_{2,3} inverted; T₄ diphasic.

Roentgen-ray of chest, wrist, thigh, feet, forearm, legs, abdomen was essentially negative. Radiographic examination of the teeth revealed chronic apical abscesses of the first and second lower left molars.

Clinical course: The temperature fluctuated between 100° and 104° until the last week of life when it varied between 96° and 99°. The pulse remained proportional to the temperature elevation until the last week of life when it became relatively very rapid. Similarly, the respirations ranged between 20 and 28 until the last week when they varied between 48 and 60. The blood pressure varied between 118 and 130 systolic and 70 and 100 diastolic throughout the whole course. On May 5, a systolic pulmonary murmur appeared and this persisted until the very end. On May 9 (about 11 days after admission) several pin-head to pea-sized nodules were felt on the dorsum of the left forearm, and the posterior surface of the left leg. They were not tender. These nodules became progressively more numerous and larger, later appearing in the right supraclavicular area, and later felt along the course of the larger vessels of all four extremities. Three days after their appearance, biopsy of some of these nodules was performed and showed the following:

The specimen is that of subcutaneous tissue and accessory skin structures. The arteries show extensive infiltration of their walls with numerous polynuclears and round cells as well as occasional eosinophiles. The inflammatory cells extend through the adventitia into the subcutaneous fat. The intimal lining is proliferative and in a few areas the medial coat shows necrosis. Some of the arterioles are filled with thrombi.

Although the infiltration involves all layers of some of the vessels, giving the lesion the appearance of a panarteritis with complicating arteriole thrombosis, the characteristic medial necrosis of so-called panarteritis nodosa can be demonstrated in only a few of the vessels. Although the entire picture is highly suggestive of panarteritis nodosa, one cannot make this diagnosis with certainty from a study of this specimen.

Impression: Thrombo-arteritis (probably panarteritis nodosa). Thus the pathological report confirmed our clinical diagnosis.

On May 20, the patient complained of tingling in the finger tips of the left hand, followed on the next day by numbness of the right foot and numbness of the first three fingers of the right hand. Examination at this time revealed atrophy and weakness of both lower extremities, edema of the feet, diminished tactile sensation of the feet, and right foot drop. On June 4 (one week before death) he complained of numbness of the middle three fingers of the right hand and index finger of the left. There was poor coöperation, the patient was inattentive and appeared exhausted. Horizontal nystagmus appeared for the first time. The reflexes showed a hyperreflexia of the upper and lower extremities. Babinski negative. Abdominal reflexes were diminished. There was diffuse symmetrical muscle wasting and atrophy, greater on the right. There was marked wasting of the muscles of the lower extremities. There was lack of concentration, but sensation seemed grossly intact except in both

feet in which there was loss of position sense, marked diminution in tactile sensibility, and diminution of pain sense.

On June 2, the patient suddenly became dyspneic, respirations became very rapid with dilatation of alae nasi. Heart was rapid with a gallop rhythm. Many fine moist râles were present at bases of both lungs. The liver was large, four fingers below the costal margin, and there was marked pretibial and sacral edema.

These symptoms and findings persisted until death occurred on June 11.

Necropsy, Case 4. General: The body is that of a well-developed and well-nourished negroid adult male. There is a wound of a recent skin biopsy on the right forearm (figure 4).



FIG. 4. Biopsy section of the subcutaneous nodule of the right forearm showing a platelet thrombus (A) occupying the lumen (B) of an artery, the wall of which (C) shows characteristic panarteritis. Many of the infiltrating leukocytes are eosinophiles. (170 X.)

Cavities: Peritoneum contains 300 c.c. of clear yellow fluid. The entire right side is occupied by liver. Pleural cavities are filled with serous fluid. Pericardial cavity contains an increased amount of fluid.

Cardiovascular system: Heart weighs 360 gm. The chambers are dilated and the apex is rounded. Myocardium shows cloudy swelling and recent platelet thrombosis between pectinate muscles of left ventricle. Aorta shows patchy atheroma.

Respiratory system: Bronchi are filled with froth. Lungs show lobular pneumonia and chronic passive congestion.

Gastrointestinal system: Ileum (distal segment) contains a large amount of dark blood. Appendix (especially the submucosa) presents vascular changes characteristic of the acute phase of periarteritis nodosa with the usual medial necrosis.

Spleen weighs 75 gm. and is fibrotic. Two accessory splenules are present, one of which is embedded in the tail of the pancreas.

Pancreas weighs 135 gm., shows considerable fibrosis and obliterative intimal proliferation of arterioles. The tail contains an accessory splenule.

Biliary system: Liver weighs 1710 gm. After being severed from its attachment the organ shrinks to approximately half of its original volume. It is mottled deep red and yellow (figure 5). The red areas are suggestive of hemorrhagic in-

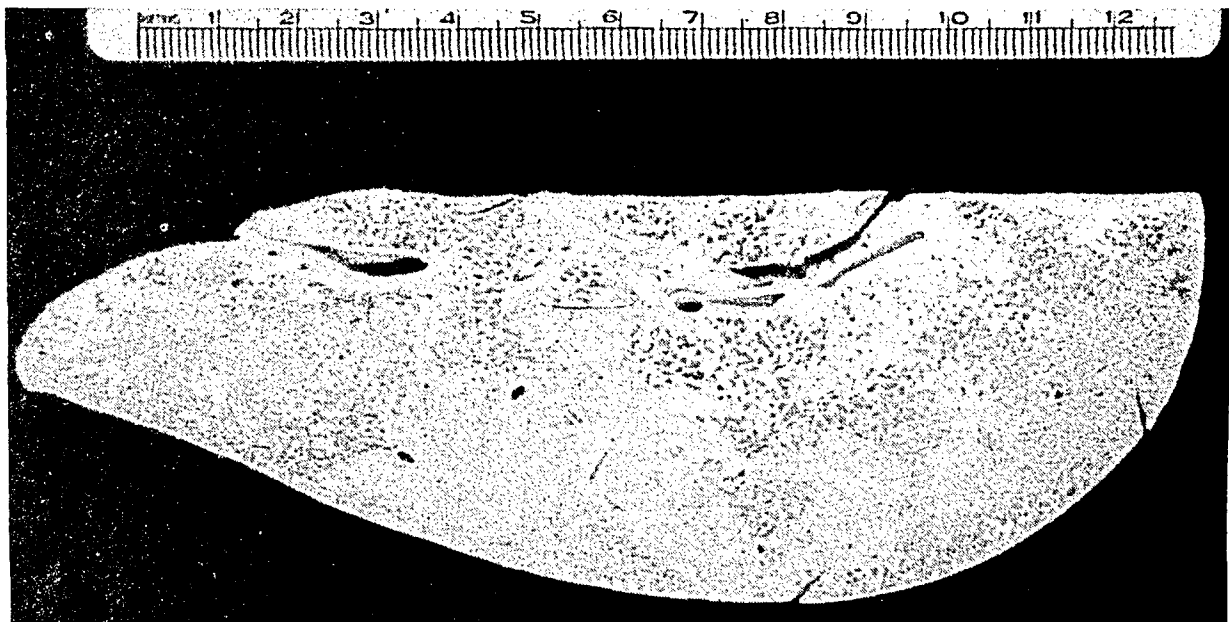


FIG. 5. Cut surface of the liver of case 4, showing distinct mottling (red and yellow), some of the areas suggesting infarcts.

farcts and are found mainly in the vicinity of portal channels in which the hepatic arteries present all stages of healed panarteritis, ranging from intimal thickening to almost complete fibrous obliteration of lumina. Some vessels also show aneurysmal dilatations.

Gall-bladder wall, especially the serosal layer, shows marked fibrosis and healed vascular lesions similar to those described in the liver.

Urinary system: The left kidney weighs 160 gm. and the right 180 gm. The capsule of each strips with difficulty leaving yellow-gray areas of fresh and old infarcts. Thrombi of various sizes fill lumina of arteries, some of which present aneurysms (figure 6). These vessels reveal all stages of acute, subacute and chronic panarteritis (figure 7). Fibrosis extends from arteries to surrounding framework. The tubules are filled with hyaline casts. Only occasional glomeruli show fibrosis. Ureteral walls are thickened to 3 mm. at their vesical orifices. Bladder is normal.

Genital system: Prostate is enlarged and shows subacute and healed stages of panarteritis. Testes show areas of fibrosis secondary to healed vascular lesions of panarteritis. Vas deferens shows recent and old panarteritic lesions.

Endocrine system: Adrenals weigh 14 gm. Peri-adrenal fat shows vessels with acute panarteritis.

Central nervous system: Brain shows numerous pontine vessels which are filled with red cell thrombi. Spinal cord shows hemorrhagic extravasations in the anterior horns involving many neurons.

Skeletal system: Quadriceps femoris muscle shows perivascular plasma and round cell infiltrations. Tendon of Achilles shows obliterative, intimal proliferation of arterioles.

Anatomical diagnosis: (1) panarteritis nodosa (acute and healed); (2) lobular pneumonia (terminal); (3) cardiac hypertrophy and dilatation; (4) mural thrombosis of left ventricle (terminal); (5) chronic passive congestion of viscera; (6) multiple serous effusions; (7) intestinal hemorrhage; (8) accessory splenules, multiple.



FIG. 6. Cut surface of the kidney of case 5. Small arrow points to thrombi occluding branches of the renal artery and hemorrhagic infarcts. The large arrow points to an aneurysm in one of these arteries.

Summary, Case 4: Young adult had sore throat three and a half months before admission followed in two weeks by pain in both legs and left wrist.

Examination revealed marked tenderness in both calf muscles with some weakness in the extremities. During his stay of six weeks in the hospital, he had fever (100° to 104°) until one week before death when temperature became subnormal; nodules appeared on all four extremities, and in the right supraclavicular area; sensory changes appeared in both hands and feet, and finally bilateral foot drop and muscle atrophy.

Laboratory examination: The blood pressure was normal. The urine always contained albumin, numerous red blood cells, hyaline and granular casts. The blood chemistry remained normal until four days before death when there was a definite elevation of urea nitrogen (45.4 mg. per cent) and creatinine (3.3 mg. per cent). Blood examination revealed a progressive anemia, hemoglobin decreasing from 75 per cent on admission to 40 per cent; red blood cells from 3,680,000 to 2,600,000; white

blood cells varied between 14,200 and 28,800; polymorphonuclear neutrophils 76 to 89 per cent; eosinophiles 1 to 7 per cent. Sedimentation time was constantly increased. The electrocardiograms always showed definite evidence of ventricular myocardial damage.

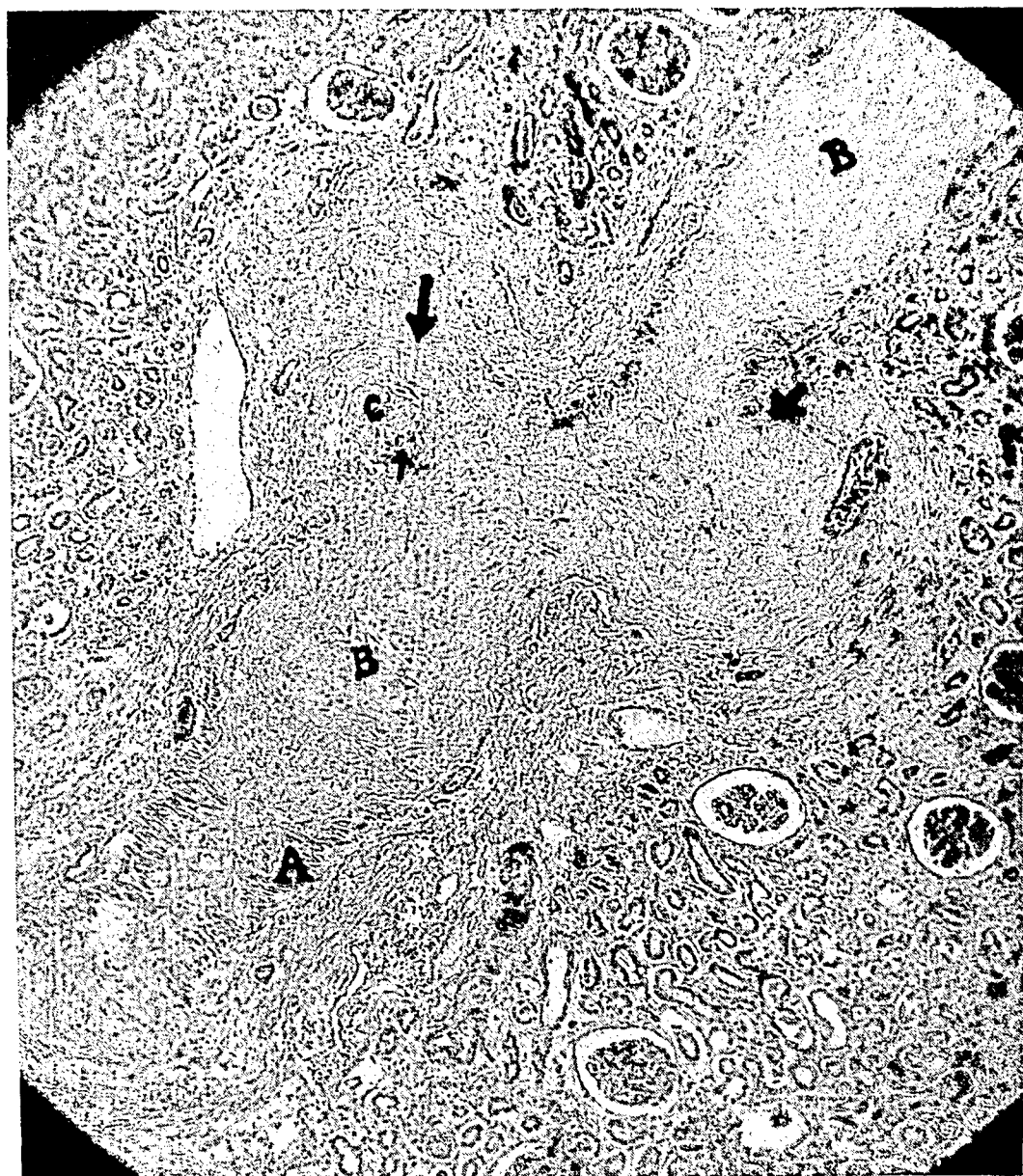


FIG. 7. Representative section through an artery of the cortex of the kidney of case 4 characterizing the healed stage of the obliterative arteritic lesion. Note fraying and marked thinning (large arrow) of the medial coat (*A*) at sites of aneurysm. One of these aneurysms is occupied by a giant cell (small arrow) granulomatous process (*C*). The rest of the lumen is completely replaced by hyalinized fibrous tissue (*B*) which also produces nodular thickening of the vessel wall. (100 \times .)

Autopsy revealed changes of panarteritis involving the appendix, liver, gall-bladder, kidney, prostate, testicles.

Case 5. A. K., 35 year-old cook, was admitted May 21, 1937, died June 15, 1937.

Chief complaint on admission was generalized weakness of seven months' duration. She was in excellent health until seven months before. At that time she first noticed

weakness and became tired doing her work. These symptoms increased in intensity so that she was compelled to resign from her position. At this time, a cough developed associated with a slight amount of expectoration, and it persisted to the time of admission. She noticed that she began to lose weight and had drenching night sweats. Three months before admission, chills, occurring every third day and followed by drenching sweats, developed and continued until the present time. Accompanying these were frequency and urgency of urination and pain in the left lumbar region and groin. In addition, she had trouble with her eyes (photophobia, lacrimation, redness). During the entire course of her illness she had occasional abdominal cramps accompanied by vomiting. She became very irritable, crying at the slightest provocation. There was considerable epigastric burning about an hour after meals. About one month prior to admission, she noticed aching, weakness, numbness, and tingling of both arms and legs. There were frequent, severe headaches. She began losing her hair and observed that her hair was turning gray. These symptoms increased in severity so that in March 1937 she was removed to a hospital where she remained for one month, but no definite diagnosis was made and as she continued to become weaker, she went home. In her previous history there was a story of jaundice as a child in Finland. At the age of 19, she was told she had a gastric ulcer. At the age of 33 she was treated for "neuritis" of the right arm. She denied venereal disease. Was married for 12 years but never pregnant.

Physical examination: Adult white female, fairly well-nourished, pale, slightly puffy, looked acutely ill. There was definite evidence of loss of weight. There was severe muscle tenderness scattered over the entire body. Pupils reacted to light and accommodation, the left pupil was slightly irregular. No ocular palsies. Lid and bulbar conjunctiva injected. There was some circumcorneal injection. The right disc was blurred, the arteries narrowed, the veins engorged, and the macular region reddish. The left disc outline was clearer, the arteries narrowed, and the veins engorged. On the temporal side, about a disc distance from the disc, was a white area surrounded by pigment. No nodules were seen on the vessels. Ears and nose were negative. Teeth were in good condition, tongue clear and moist, pharynx injected. There were no palpable glands in the neck. The point of maximal impulse was in the fifth left intercostal space within the midclavicular line. There was regular sinus rhythm. Sounds were of good quality. There were no murmurs at the apex or base. The second aortic sound was equal to the second pulmonic. The lungs were clear. Liver and spleen were not felt. There was a bilateral foot and wrist drop with extreme tenderness over these extremities, especially on the right. Neurological examination: There was the peripheral type of long-stocking and long-glove sensory involvement. The deep reflexes were normal. The Babinski reflex was negative. There was some impairment of motor power with considerable pain and tenderness present. On finger-to-nose test, there was definite incoördination. Pelvic and rectal examinations were negative.

Laboratory studies: Blood Wassermann test negative. Spinal fluid Wassermann test negative. Fluid was clear, 60 cells, chiefly lymphocytes. Colloidal gold 1111000000. Blood culture sterile.

Blood chemistry: sugar 114.2 mg. per 100 c.c., urea nitrogen 12.5 mg. per 100 c.c., cholesterol 142.8 mg. per 100 c.c., calcium 9.3 mg. per 100 c.c., phosphorus 4.8 mg. per 100 c.c., chlorides 510 mg. per 100 c.c., icterus index 5. Van den Bergh negative direct and indirect. Agglutination for typhoid, paratyphoid A and B, *B. melitensis* and *abortus* was negative.

Urine examination showed specific gravity varied from 1.010 to 1.020. Repeated specimens showed 1 to 2 plus albumin, many red blood cells, and granular casts. Phenolsulphonephthalein excretion was 15 per cent in two hours, 40 per cent in four hours. Urea clearance was 49.7 per cent. Urine was negative for arsenic and lead.

Roentgen-rays of skull, left upper and right lower extremities, and lumbar and lower dorsal spine were negative.

Roentgen-ray of chest showed no pulmonary infiltration in the upper part of the chest. The left diaphragmatic leaf was dimly visualized, disappearing within a hazy, veil-like opacity which obscured the diaphragmatic leaf as well as the left costophrenic sinus. The following possibilities should be considered: "fluid in the left costodia-phragmatic recess, splenic infarct with a reaction on the pulmonary side of the diaphragmatic leaf. In view of the absence of consolidation anywhere in the chest, it is highly improbable that we have to deal with pleuro-pulmonary pathology."

Blood counts:

	May 21	May 25	May 28	June 2	June 15
White blood cells	14,400	14,300	12,800	9,100	6,000
Red blood cells, millions	3.6	3.68		3.46	2.94
Hemoglobin, per cent	60	68		54	40
Polynuclear neutrophiles	76	82	73	69	54
Monocytes	5	2	4	4	2
Lymphocytes	16	14	21	22	44
Basophiles	0	0	0	1	0
Eosinophiles	2	2	2	4	0

Bleeding time $1\frac{1}{2}$ minutes, coagulation time 8 minutes, fragility test .54 to .36 per cent, blood platelets 390,000.

Sedimentation time: (18 mm.) May 23, 30 minutes; May 28, 18 minutes; June 1, 23 minutes.

Electrocardiograms: *May 25.* Regular sinus rhythm, rate 140. QRS_{1,2} slurred; QRS₃ diphasic. T_{1,2} depressed; T₃ isoelectric. *May 27.* Regular sinus rhythm, rate 130. QRS_{1,2,3} slurred, QRS₃ diphasic. T_{1,2} depressed, T₃ isoelectric.

Clinical course: The temperature on admission was 101.2° and fluctuated between 101° and 104° throughout the stay in the hospital with the exception of a sudden drop on the morning of the sixth day to 98.6° and a sudden elevation on the day of death to 107°. The pulse was more rapid than the temperature warranted. The blood pressure varied between 90 and 145 systolic, and 30 and 84 diastolic. On the third day, the patient developed a gallop rhythm which persisted for five days. On May 26 she experienced fits of extreme depression alternating with fits of crying. This persisted for several days. Three days after admission, a few pin-head-sized nodules were felt in the popliteal fossae, and later additional ones were palpated along the large vessels of the forearms. Two weeks after admission, the liver became palpable two fingers below the costal margin. One week before death there was complete loss of position and tactile sense in her lower extremities. There was ankle and pretibial edema. Three days before death she became extremely cyanotic, was euphoric, incoherent, and exhibited echolalia. The abdomen was markedly distended. The liver was three fingers' breadth below the costal margin, whereas the spleen could not be felt. The face was puffy. On the day of death, the temperature rose to 107°, the heart sounds were very rapid and distant, and there were fine twitchings of the muscles of the face. The pain in the legs was excruciating, and tenderness on pressure remained constant throughout the course of her stay at the hospital. She died on June 15 from cardiac failure.

Necropsy, Case 5. General: The body is that of a well-developed and moderately under-nourished white female. There is a biopsy scar over the right deltoid region.

Cavities: The right pleural space contains old, and the left, recent adhesions. The visceral and parietal pericardial linings are adherent and show acute fibrinous inflammation. The mediastinum contains a dense mass, 4 by 3 by 2 cm., situated between the aorta and left main bronchus (figure 8). The mass is firmly adherent to both structures, follows along the aorta, and on section presents a firm gray and

yellow appearance. Microscopically, it is a granulomatous mass which contains areas of necrosis, fibroblastic proliferation, few multinucleated giant cells, suggestive epithelioid cells, hyalinization of fibrous tissue and perineural infiltration (figure 9).

Cardiovascular system: Heart weighs 500 gm. Myocardium is flabby and shows cloudy swelling. Aorta shows patchy atheroma.

Respiratory system: The medial border of the upper lobe of the left lung is in anatomical continuity with the mediastinal mass, the lung parenchyma showing caseous

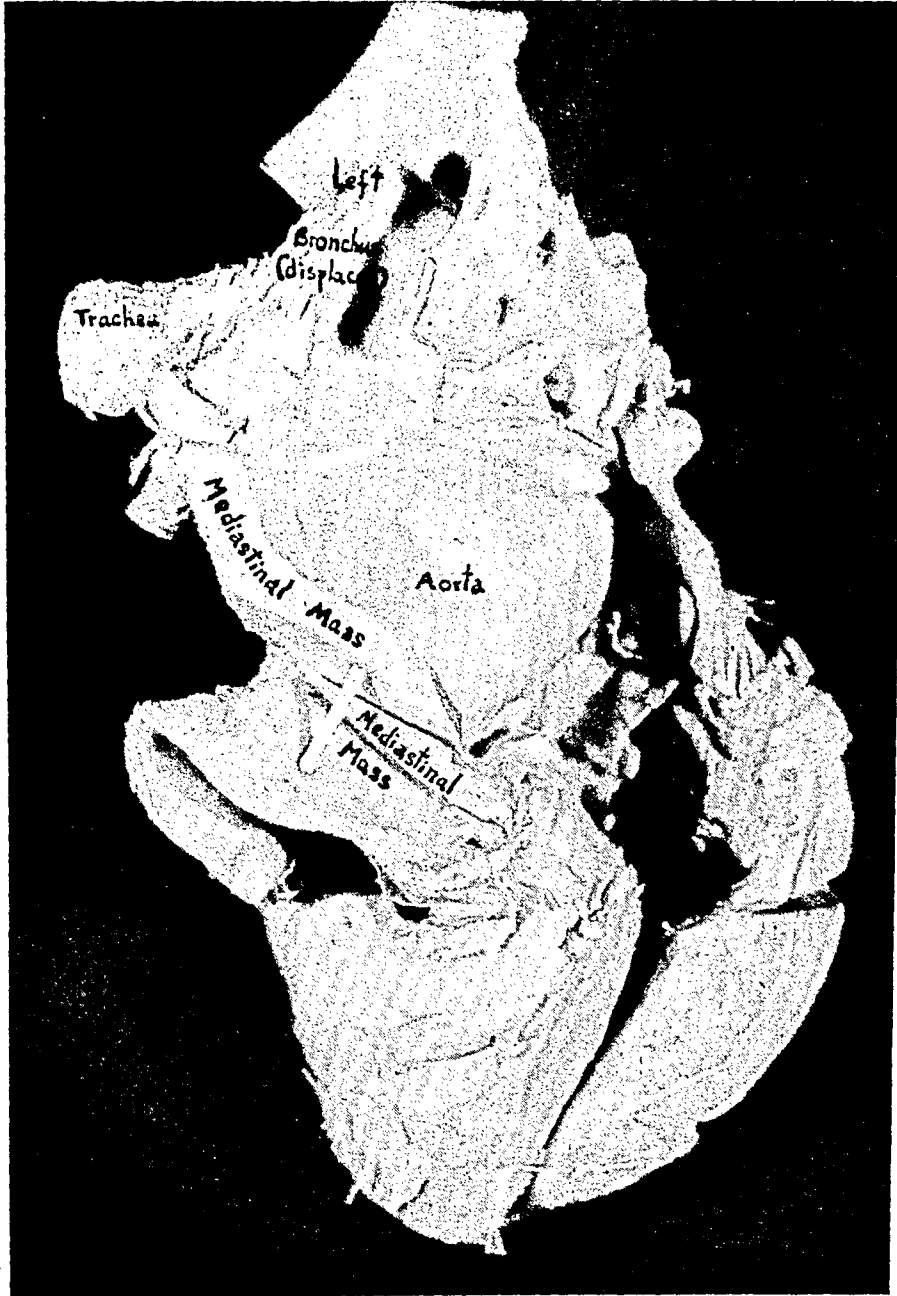


FIG. 8. Heart and mediastinal mass between left bronchus and aorta, of case 5. The aorta is almost entirely encircled by the granulomatous mass. The trachea and bronchi are here shown displaced in order to bring the relationship of the mass into better view.

necrosis as well as epithelioid and giant cell reaction (figure 10). The left lower lobe anteriorly shows thrombosis and infarction with superimposed suppuration. Other areas show fibrous replacement and calcification of parenchyma, chronic passive congestion, and lobular pneumonia. Blood vessels show proliferative vascularized subintimal connective tissue with narrowing of the lumena and infiltrative changes in the media and adventitia.

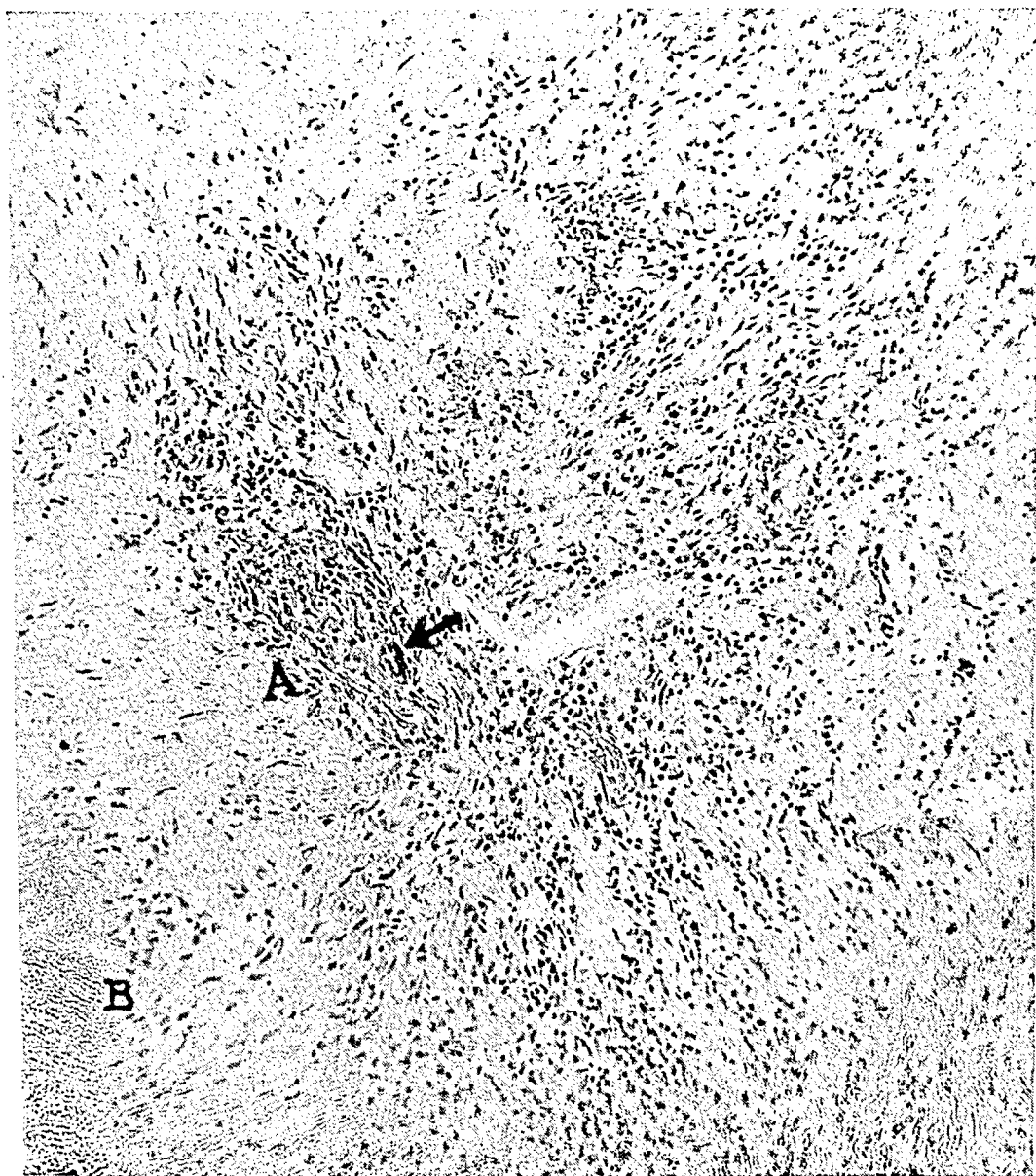


FIG. 9. This is a section through a representative portion of the mediastinal mass of case 5. Note the marked fibroblastic reaction and hyalinization (*A*), the areas of necrosis (*B*), and multinucleated giant cells (arrow) surrounded by groups of elongated epithelioid cells. (210 X.)

Gastrointestinal system: Esophageal wall presents an occasional small artery which is the seat of perivascular infiltration. Vermiform appendix presents a characteristic argentaffinoma.

Spleen weighs 210 gm. and shows marked perisplenitis. The parenchyma reveals infarction, suppuration, tubercle-like lesions with giant cells resembling tuberculosis,

and necrotizing central arteriolitis. Some of the central arterioles show giant cells and granulomatous changes in the intima (figure 11).

Pancreas weighs 135 gm. The vascular changes consist of granulomatous thrombo-arteritis with giant cells and epithelioid cells, the lesions being those of acute and healed panarteritis. One vessel shows a "tubercle-like" structure in the wall.

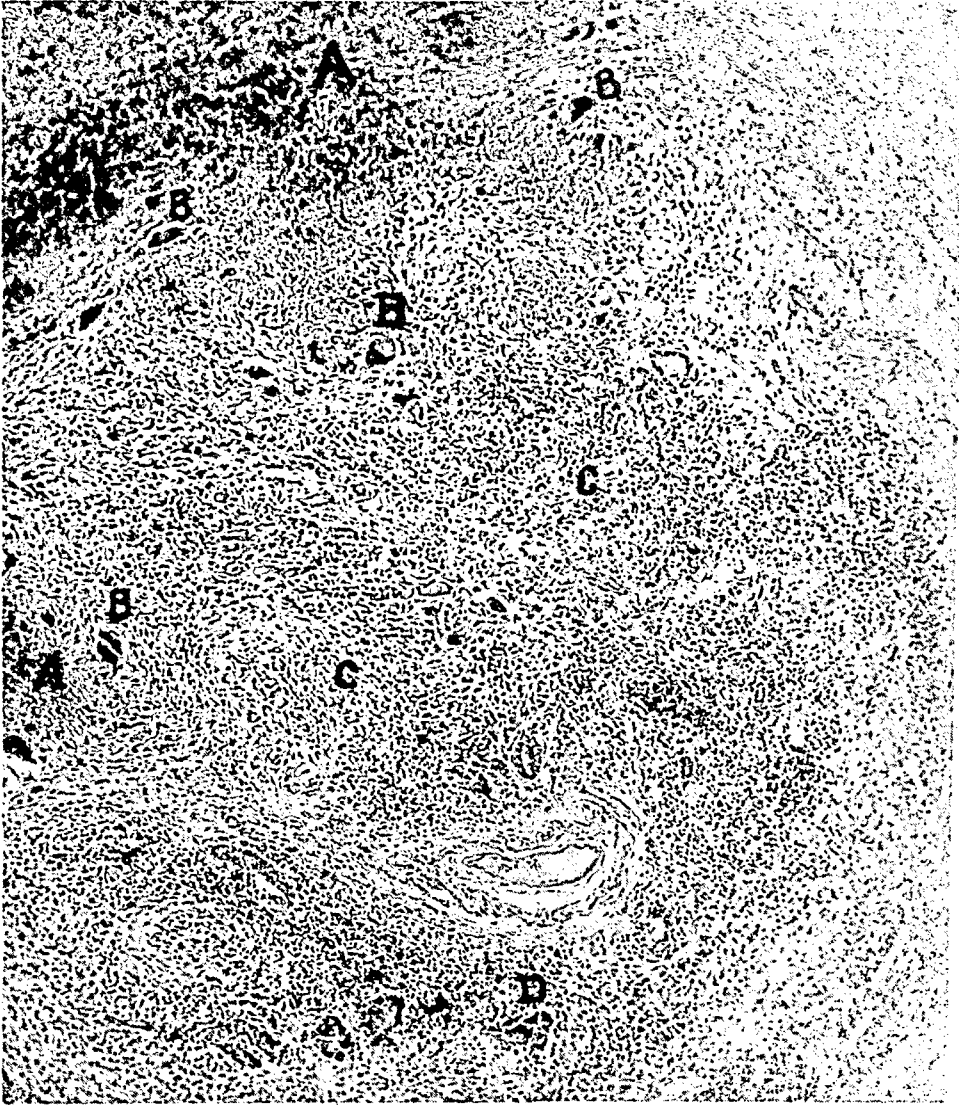


FIG. 10. Section of lung of case 5, taken through the medial border of the left upper lobe, where the latter merges with the mediastinal mass. Note the caseous necrosis (*A*) with a peripheral zone of Langhans giant cells (*B*) directly continuous with the granulomatous structure (*C*). The latter, in turn, is in anatomical continuity with atelectatic lung and bronchioles (*D*). (130 X.)

Biliary system: Liver weighs 2280 gm. and shows marked congestion and focal hemorrhagic necrosis.

Gall-bladder wall shows healed and granulomatous vascular lesions. The lumen of the viscus and its duct contain small calculi.

Urinary system: Kidneys weigh 230 gm. each and show subacute nephritis with

atypical crescents, interstitial edema and leukocytic infiltration. Tubules contain blood and polynuclear cells. In areas the stroma contains epithelioid and giant cells. Some of the arcuate arteries are thrombosed with only an occasional infarct. Ureters and bladder are normal.

Genital system: Uterus shows vascular changes of granulomatous thromboarteritis similar to those observed in the other organs.

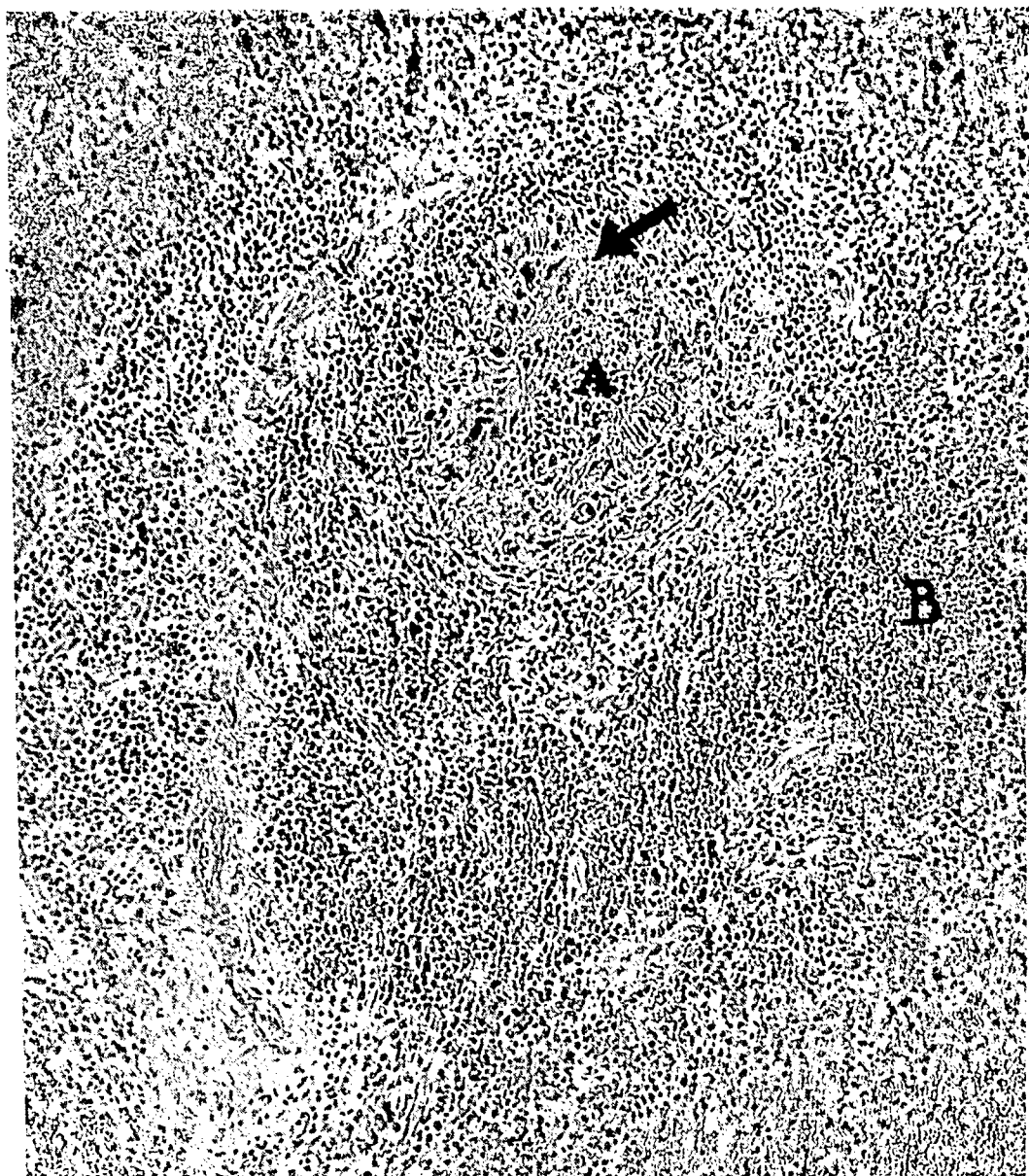


FIG. 11. Section of spleen of case 5, through a corpuscle showing Langhan's giant cells (arrow) replacing its germinal center. Also, note incipient acute inflammatory infiltrate (A) which becomes much more marked in the pulp (B) and which also assumes a suppurative character in other portions of the spleen. (200 X.)

Lymphatic system: Mediastinal lymph nodes are involved in the mass described under mediastinum, and show the same histopathologic changes found in the mass.

Endocrine system: Adrenals show tubercle-like lesions in the capsules and marked vascular changes consisting of acute and granulomatous panarteritis with thrombosis. The vessel walls contain epithelioid and giant cells, and areas of necrosis of the media,

although the latter is not as extensive as usually seen in the acute phase of periarteritis nodosa (figure 12).

Skeletal system: Sections of diaphragm and pectoralis muscle show healed panarteritis. The pectoralis muscle also contains encysted trichinae.

Central nervous system: Brain shows congestion and edema.

Bacteriology: Stains of the sections and direct smears of organs are negative for tubercle and leprosy bacilli as well as for spirochetes.

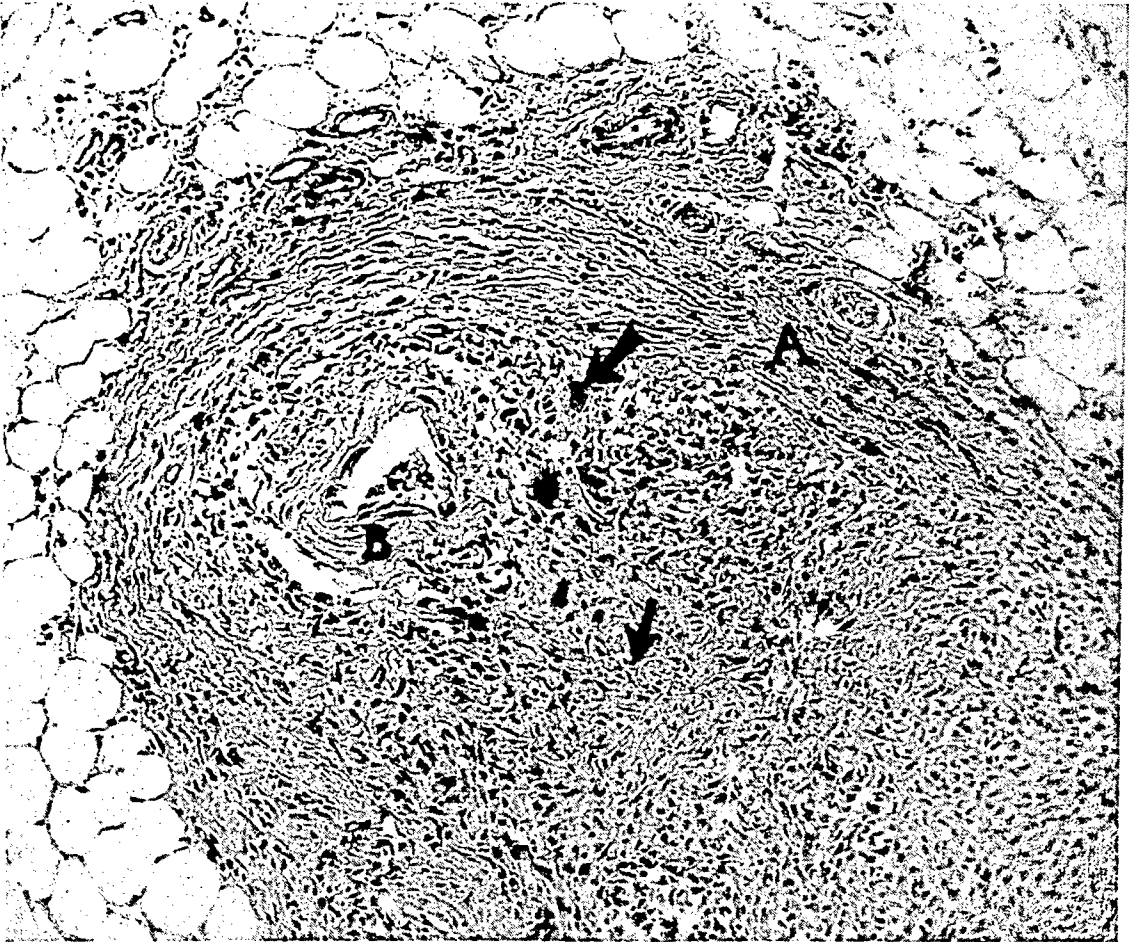


FIG. 12. Section of periadrenal tissue of case 5 showing granulomatous structure and giant cells (arrows) replacing the lumen and wall (A) of a small periadrenal artery. Note attempt at recanalization (B) of the occluded lumen. (200 X.)

Anatomical diagnosis: (1) Panarteritis, granulomatous (etiology undetermined); (2) granuloma of mediastinum and lung; (3) multiple visceral infarcts; (4) subacute glomerulonephritis; (5) lobular pneumonia (terminal); (6) cardiac hypertrophy and dilatation; (7) chronic passive congestion of viscera; (8) argentaffinoma of appendix; (9) chronic cholecystitis and cholelithiasis; (10) trichiniasis (encysted); (11) deltoid scar (biopsy).

Summary, Case 5. Adult female, 35 years of age, was admitted with complaints beginning seven months before admission consisting of weakness followed by cough, loss of weight, night sweats, chills, frequency and urgency of urination, eye signs (photophobia, lacrimation, redness), recurrent abdominal cramps, extreme irritabil-

ity, aching, weakness, numbness and tingling of both arms and legs, frequent severe headaches, hair turning gray with some loss of hair.

Repeated examinations revealed a fairly well-nourished and pale female, progressively losing weight. The heart exhibited a gallop rhythm and gradually grew weaker. There were psychotic changes. A few nodules were palpable in the popliteal fossae and along the large vessels of the forearms. The abdomen was markedly distended, and the liver was enlarged. There was ankle and pretibial edema. There was severe muscle tenderness all over the body, most intense over the lower extremities. There was bilateral foot and wrist drop with peripheral type of long-stocking and long-glove sensory involvement. Fever, leukocytosis, anemia, and increased sedimentation rate were present. Repeated urine examinations showed albumin, casts, and red blood cells.

Autopsy revealed the following: A granulomatous lesion in the mediastinum and left lung. Changes characteristic of panarteritis nodosa in the lungs, spleen, pancreas, liver, gall-bladder, kidneys, uterus, adrenals, diaphragm, and pectoral muscles. Encysted trichinae in the pectoralis muscle.

Clinical Symptoms and Signs in Cases Reported: Cases included three males and two females. The age of the patients varied from 25 to 49 years. This series showed an average duration of five months from the onset of symptoms to death.

Summary of Symptoms and Signs in Five Cases of Periarthritis Nodosa:

Fever.....	4	Abdominal pain.....	3	Dyspnea.....	2
Albuminuria.....	4	Pain in extremities.....	3	Subcutaneous nodules....	2
Hematuria.....	4	Foot drop.....	3	Purpura.....	2
Edema.....	4	Loss of weight.....	3	Headache.....	1
Hepatomegaly.....	4	Tingling sensation in		Pain in chest.....	1
Leukocytosis.....	3	extremities.....	2	Atrophy.....	1
Eosinophilia.....	3	Visual disturbances.....	2	Cyanosis.....	1
Chills.....	3	Cough.....	2	Icterus.....	1
Weakness.....	3	Vomiting.....	2	Splenomegaly.....	1
Hypertension.....	3	Sweats.....	2	Positive Wassermann.....	0

GENERAL DISCUSSION ON THE PATHOLOGICAL FINDINGS OF THIS SERIES OF CASES

The numerous and varied pathological changes observed in these cases compare favorably with the findings of previous observers. It seems advisable to note, although at the risk of repetition, that the findings described above have, as a common underlying process, an arteritis. This arteritis is found in acute, subacute or chronic phase. Frequently two, or all three stages are demonstrable in the organs of the same case, even in the same organ. Equally frequent in occurrence are the findings representing the various complications of arteritis which one would logically expect to encounter. They are (1) necrosis of vessel wall with hemorrhage, recent or old; (2) thrombosis of arteries with hemorrhagic or anemic infarctions, recent and old; (3) aneurysmal dilatation of arterial walls with secondary changes, such as hemorrhage, due to rupture, pressure necrosis of surrounding tissue; and, finally, (4) replacement fibrosis of thrombi as well as of the tissues destroyed by the above described secondary changes. The reparative process of recanalization of thrombi, although described frequently, is not a prominent feature of the later changes observed in this series of cases.

A little more detailed analysis of our findings reveals several additional features worthy of note, the most interesting one of which is provided by case 5. In this case, the mediastinal granuloma and the giant cell reaction are intriguing findings. The gross character produced by the dense fibrosis in the mediastinal mass, the caseous necrosis and giant cell reaction in the lung, the miliary abscesses and giant cell reaction in the spleen have led noted pathologists who were shown the specimens to suggest a number of possible etiological agents among which may be mentioned syphilis, tuberculosis and Hodgkin's disease. One keen clinician even suggested the possibility of leprosy. However, to date none of these suggestions could be confirmed. Parasitic etiology was considered early in the study of the case as a possible explanation for the granulomatous changes in the lesions but with unsuccessful attempts at proof, although, strangely enough, encysted trichinae were found in the pectoralis muscle. However, the relative frequency of occurrence of this lesion to which the recent literature calls attention, adds little support to trichiniasis being the causative agent in this particular case.

In discussing the etiology of this disease, the above-described cases provide much food for thought. One cannot refrain from considering the etiology of this disease to be almost as protean in nature as are the varied anatomical changes. In addition to a possible underlying syphilis, Hodgkin's disease, tuberculosis, leprosy and parasitic infestation, mentioned in the study of case 5, one may consider the intense polymorphonuclear cell reaction and occasional suppuration as evidence of a non-specific pyogenic agent, whereas the abundance of eosinophiles may be considered an expression of allergy, rather than that of a parasitic infestation. With the exceptional granulomatous changes observed in case 5, as well as the varied findings observed in the other cases in this series, it is obviously very difficult to determine any pathognomonic histopathologic changes which might point to the causal agent in any given case. It is very likely that the secondary and complicating or coincidental changes (unrelated to the disease) so disguise the picture as to make the recognition of a specific histopathology of a "pure" case of this disease well nigh impossible. Many of the unexplained fibrosed or recanalized blood vessels which, in the past, have been encountered in routine postmortem examinations and biopsies and which have been previously brushed aside for want of explanation, may have been healed lesions of panarteritis of varying degree (caused by various agents) which had existed as localized lesions or unrecognized during life.

It is also worthy of note that varying degrees of cirrhosis of the liver were present in all cases of this series. The process most likely represents healed lesions of panarteritis. Although acute changes were not demonstrable in all of the cases, the scarring, which contributed to the cirrhosis and which most probably represents old healed lesions, was a constant finding.

The lobular pneumonia which was found in most of the cases appears to be a terminal event and without any special significance.

The presence of hyperplastic splenic tissue (accessory splenules and splenomegaly) also seems unrelated to the disease.

Finally, it may be mentioned that this series of cases afforded the rare opportunity to study the changes in the central nervous system. The thrombus in the left internal carotid artery and the changes which it produced in the left frontal lobe of case 1 are of special interest in this regard. The somewhat similar findings in the smaller vessels of the pons in case 4, as well as the multiple hemorrhages observed in the spinal cord, lead one to conclude that the central nervous system is not spared in this disease.

DIAGNOSIS

Many authors have attempted to present a symptom complex as diagnostic of the disease, varying from the triad of symptoms, "chlorotic marasmus," polymyositis and polyneuritis, and gastrointestinal symptoms to a sextet of symptoms: gastrointestinal, renal, neuromuscular, cardiac, cerebral, and cutaneous, to the unstated number of symptoms based on vascular disturbances in the particular organs or regions affected. Thus, the complexity of the clinical picture is apparent. The diagnosis of periarteritis nodosa is to be considered in any continued illness, and while the symptoms may be related to all the organs involved, no symptoms of the disease may be present as in our case 2.

In the 106 cases reported in the English literature a correct antemortem diagnosis was made in 30, including four of our five cases. In some instances, the diagnosis may be verified by biopsy of a subcutaneous nodule or muscle, examination of a surgical specimen, or laparotomy.

PROGNOSIS AND TREATMENT

Harris, Lynch, and O'Hare³ in reviewing the 101 cases reported in the English literature state that nine of those patients may be alive and five are definitely known to be alive. A patient may survive periarteritis nodosa if the disease remains localized in some organ such as the appendix or, if in a vital organ, progresses to the healed stage without producing functional insufficiency. All our cases died. There has been no specific treatment that has had any success at the present time. Symptomatic therapy should be used.

SUMMARY

Five cases of periarteritis nodosa are reported four of which were diagnosed ante mortem.

The clinical picture and autopsy findings are presented in all five cases.

REFERENCES

1. VON ROKITANSKY, C.: Ueber einige der wichtigsten Erkrankungen der Arterien, Denkschr. d. k. Akad. d. Wissensch., 1852, iv, 49.
2. KUSSMAUL, A., and MAIER, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarthritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsch. Arch. f. klin. Med., 1866, i, 484.
3. HARRIS, A. W., LYNCH, G. W., and O'HARE, J. P.: Periarthritis nodosa, Arch. Int. Med., 1939, lxiii, 1163.

THE CLINICAL VALUE OF STERNAL BONE MARROW PUNCTURE*

By THEODORE H. MENDELL, M.D., DAVID R. MERANZE, B.S.
(CHEM.), M.D., and THEODORE MERANZE, M.D.,
Philadelphia, Pennsylvania

IN the past decade the introduction and widespread application of sternal aspiration for the study of the living bone marrow have given the clinician a simple and practical method of studying hemopoiesis during life. This method of examining bone marrow has come into favor because of the ease of securing material and the great value of the information obtained. Bone marrow biopsy, although preferable to the simple aspiration method because the marrow architecture is preserved, is a surgical procedure requiring an operating room set-up and several days for the preparation of the material. Sternal puncture, on the other hand, is a simple bed-side procedure, easily tolerated by the patient, and in most instances it yields sufficient information for diagnosis. Occasionally repeated punctures may be necessary in a given case before a correct diagnosis can be made, but as a rule no ill effects are caused patients by such repetitions. This ease of performance, the satisfactory material obtained, and the fact that the composition of the sternal marrow may be taken as representative of the whole mass of the hemopoietic tissue, make sternal puncture an acceptable method for studying living bone marrow in all its phases. Scott,¹ in his excellent monograph on the subject best summarizes its value when he states: "sternal marrow puncture provides an opportunity of hematologic education which has never previously existed, it is in Schulten's words: 'die Hochschule für den Haematologen.'"

Very little was known about the physiology of bone marrow until the time of Neumann's² investigations in 1868 when he showed that the marrow was the site of erythropoiesis. In the following year he demonstrated that it was also the site of leukopoiesis. Before these investigations the bone marrow was regarded merely as a mechanical filler of the medullary cavities of bones. The studies of bone marrow changes during disease which followed Neumann's work were not satisfactory because the material was obtained at postmortem examinations and hence did not portray living hemopoiesis. The study of the human marrow during life was instituted in 1908 by Ghedini⁴ who performed biopsies of the tibial marrow for the diagnosis of malaria. However, it was not until 1923 that Seyfarth⁵ suggested trephining the sternum for the study of bone marrow. The technic used by him required a surgical set-up and accordingly did not come into common use until Arinkin's^{6,7} important works in 1927 and 1929. He was the first

* Received for publication September 25, 1940.
From the Wards and Laboratories of the Mount Sinai Hospital, Philadelphia, Pa.

to "needle puncture" the outer plate of the sternum, aspirate marrow, make smears, and study living bone marrow. Since his reports there have been numerous other investigations which have corroborated the conclusions reached by him and which have reëmphasized the value and importance of sternal puncture. In the recent papers of Scott¹ and Vogel, Erf, and Rosenthal² the subject is completely reviewed.

Many workers have stressed the superiority of sternal trephine over aspiration. Our experience, however, indicates that the ease of performance and the sufficiency of information gained from sternal aspiration in most cases make it the method of choice as a routine procedure. If the desired information is not obtained by aspiration, trephine or biopsy can be performed. In only a few cases have we been unable to obtain marrow material for diagnosis by aspiration, so that we now limit the surgical procedure of trephining to cases from which no diagnostic marrow can be obtained by sternal puncture. This has occurred twice in 300 sternal aspirations: (1) A 67-year-old male who presented a leukemic peripheral blood picture (11,500 leukocytes with 27 per cent myelocytes) and who yielded a "dry" sternal puncture. Subsequent studies proved this to be a case of Albers-Schoenberg's disease with no normal marrow cavities. (2) A 48-year-old female whose "dry" sternal aspiration was owing to the presence of an aplastic anemia with dense sclerosis of the bone marrow. We feel, therefore, that only in instances in which aspiration yields no marrow or where insufficient information is obtained by aspiration is sternal biopsy indicated.

Sternal marrow puncture is indicated in all cases suggesting disorders of the blood forming organs or reticulo-endothelial system, or whenever the clinician seeks to follow hematopoiesis during life. It is indispensable in the diagnosis of blood dyscrasias, or when such a diagnosis must be excluded.

This report was prepared to analyze our experiences with sternal puncture during the past three years. Our purpose was three-fold: (1) to re-determine for ourselves and to check, if possible, the criteria of normal sternal marrow as laid down by other authors, particularly those which have appeared in the literature during the past few years; (2) to study the marrow of all cases showing or suspected of suffering from blood dyscrasias or disorders of the reticulo-endothelial system, and (3) finally to correlate, if possible, such marrow findings with the underlying disease process.

We have selected as our "normal" group patients entering the hospital with no evidences of blood dyscrasias or of disturbances of the reticulo-endothelial system. These patients were admitted for conditions which in no way affected hematopoiesis and were unassociated with bleeding or fever. Patients with functional disorders made up the bulk of this group, namely: cases of neuroses, hysteria, spastic neurogenic colon, cardiospasm, and cases admitted for observation which after complete investigation proved to be free of any organic ailment. Other "normals" included cases of uncomplicated diabetes mellitus, diabetes insipidus, uncomplicated hernias prior to operation, undescended testicle, visceroptosis, uncomplicated peptic ulcer, etc.

There were 115 cases in this "normal" group; their ages ranged between 15 and 50 years.

Method of Sternal Puncture. Jaffe⁹ and others have shown that the larger the quantity of marrow material aspirated the greater is the dilution of this material with peripheral blood from the marrow venous sinuses. On the other hand, the smaller the quantity aspirated the greater is the concentration of marrow proper obtained for study. We have accordingly employed the method limiting the aspiration to 0.1 to 0.2 c.c. of marrow material. With the patient flat on his back, 0.5 c.c. of $\frac{1}{2}$ per cent novocaine solution is injected intracutaneously and subcutaneously over the sternum in the midline just below the level of the second rib. After waiting one or two minutes for the anesthetic to take effect, an 18 gauge sternal puncture needle with a sharp short bevel (we used the regular Barker stainless steel spinal needle, cut down to the size of $1\frac{3}{4}$ inches for adults and to $\frac{1}{2}$ to $\frac{3}{4}$ inch for infants and children) is inserted into the anesthetized area at right angles to the sternum. A rotary drilling motion is used to penetrate the outer plate of the sternum. As the needle enters the marrow cavity an abrupt and sudden "give" can be felt by the operator. The stylette is now removed and a tight 1 or 2 c.c. syringe is attached to the needle and between 0.1 and 0.2 c.c. of marrow is aspirated. The needle with the syringe attached is then quickly withdrawn and the puncture point sealed with a drop of collodion. The entire procedure requires approximately two or three minutes. The aspirated material is then expelled on a glass slide from which smears and counts are made. The smears can be easily differentiated macroscopically from peripheral blood by the presence of visible fat globules and microscopically by the presence of immature marrow cells. The stains used were Wright's and Jenner-Giemsa, allowing double the time required for the staining of peripheral blood smears.

For our first 100 cases we counted 500 cells for each differential. Later it was found that if the smears were evenly spread the same information could be obtained by counting 200 to 300 cells. Total counts were made on each examination, but in general it was found not to be so important as the differential count, additional confirmation of the principle that diagnoses in hematology depend more on the types of cells found than on their number. The range in the total counts among our "normal" subjects was great. We found in some "normal" marrows total counts as low as 15,000 nucleated cells and in others as high as 160,000 per cu. mm. In the cases of leukemia were found, as a rule, the highest number of nucleated cells, yet in some instances of leukemia the total counts fell within the accepted normal range.

The findings in the 115 "normal" cases are given in table 1.

It is well to point out again that these values in the main agree with those reported in recent publications on this subject. In hematology much confusion exists because investigators have applied different names to the same cells and also because of the tendency to individualize relatively minor differences of perhaps doubtful significance in cellular structure. We have

TABLE I

Leukopoietic Elements:

Myeloblasts.....	1.2%
Promyelocytes.....	0.5
Myelocytes.....	7.0
Metamyelocytes.....	12.4
Non-segmented neutrophils.....	21.5
Segmented neutrophils.....	35.7
Basophiles.....	0.2
Eosinophiles.....	2.1
Eosinophilic myelocytes.....	0.6
Hematogones.....	3.3
Reticulum cells.....	1.1
Lymphocytes.....	13.5
Monocytes.....	0.7
Plasma cells.....	0.1
Megakaryocytes.....	0.1

Erythropoietic Elements:

(per 100 white blood cell elements)

Megaloblasts.....	1.0
Erythroblasts.....	5.3
Normoblasts.....	9.1

Ratio Leukopoiesis to Erythropoiesis:

100 : 15.4

attempted to use as simple a classification as possible, employing names familiar to most clinicians as well as to the hematologists and pathologists, and have avoided as far as possible unimportant subgroups of the same cell.

Many adequate descriptions of the marrow cells are available in textbooks and recent publications. Most of the primitive cells of the myeloid series occur normally in the bone marrow and should present no difficulty in diagnosis with proper staining. We have not attempted to differentiate between myeloblasts and lymphoblasts but have depended upon the associated cell type to settle this question in the particular case studied. The promyelocyte, myelocyte, and metamyelocyte are easily recognized. The neutrophilic granulocytes are divided into the non-segmented and segmented forms. The eosinophile and eosinophilic myelocyte, the basophile, plasma cell, monocyte, and lymphocyte offer no difficulties in differentiation to anyone already familiar with smears of normal peripheral blood. The reticulum cell, "hematogone," and the megakaryocyte are never found in the peripheral blood normally. The reticulum cell originates from the reticulo-endothelial system and is a large cell possessing a granular gray blue cytoplasm with serrated margins and an ovoid nucleus. The "hematogone" is smaller than the lymphocyte, has a dense solidly staining nucleus occupying nearly the entire cell and shows very little cytoplasm. The megakaryocyte (the progenitor of the platelet) is the largest cell encountered in bone marrow. It shows a finely granular bluish cytoplasm usually with multiple purplish nuclei. Often small bodies of platelets can be seen breaking off.

In the erythropoietic series we have differentiated three principal types of cells: (1) megaloblast, (2) erythroblast, and (3) normoblast. We have made no attempt further to divide these cells into sub-groups as some others have done. These cells are not seen in the normal peripheral blood, although

in hemorrhage or other irritative states of the marrow, normoblasts may be found peripherally. Early in our studies we did routine reticulocyte counts, but later abandoned this because it afforded no helpful information and because the findings indicated that erythropoiesis could be better determined by the increase in the immature erythropoietic cell groups than by the determination of the reticulocyte activity. There are those who do not believe that the megaloblast is ever seen in a normal bone marrow and that its presence indicates pathologic erythropoiesis seen only in pernicious anemia. We, however, are inclined to agree with those who regard it as the youngest evidence of normal erythropoiesis and have, therefore, included it in our figures of normal bone marrow.

We have found useful, as have others, the ratio of leukopoiesis to erythropoiesis. In this work the normal ratio was 100:15.4. Variations from this normal ratio were found significant, as will be shown throughout this work.

Primary Pernicious Anemia: We have studied 12 cases of primary pernicious anemia. Seven were studied in the stage of relapse. These showed peripheral counts ranging between 30 and 40 per cent hemoglobin (Sahli)* and 1,300,000 to 1,800,000 red blood cells with reticulocyte counts ranging between 0.5 and 0.9 per cent. In all of these cases the bone marrow before liver therapy was begun was definitely megaloblastic. The cellularity was increased, the increase being chiefly of the immature erythropoietic elements. The ratio of leukopoietic to erythropoietic elements changed from 100:15 to 100:94. Reticulocytes in the bone marrow in relapse were too few to be counted. These findings are shown in table 2.

TABLE II

Erythropoietic Elements:

(per 100 white blood cell elements)

Megaloblasts.....	10.9
Erythroblasts.....	28.9
Normoblasts.....	54.5

In some cases, as early as 24 hours and in others within 48 hours after institution of liver therapy, the bone marrow underwent a transition from the megaloblastic to the normoblastic phase. Five patients were studied by serial sternal punctures during the course of liver therapy. Their peripheral blood counts ranged from 46 to 60 per cent hemoglobin (Sahli) with 1,900,000 to 2,700,000 red blood cells per cu. mm., reticulocytes from 7 to 20 per cent. The beginning maturation and liberation into the blood stream of the erythropoietic elements of the marrow were shown by the following alteration in the leukopoietic: erythropoietic ratio from 100:94, in state of relapse, to 100:48 during treatment, and by the rapid maturation of the erythropoietic cells to more mature forms, shown in table 3.

* Throughout this work 14.5 gm. hemoglobin are equivalent to 100 per cent hemoglobin (Sahli).

TABLE III

Erythropoietic Elements:

(per 100 white cell elements)

Megaloblasts.....	3.0
Erythroblasts.....	18.1
Normoblasts.....	27.3

Six patients were studied during remission. Several sternal aspirations were made in each case. Peripheral blood counts on these patients had reached normal, ranging from 80 to 100 per cent hemoglobin (Sahli), with red blood cell counts ranging from 4,000,000 to 5,000,000 per cu. mm. and reticulocyte counts from 1.2 to 3.2 per cent. At this phase the marrow showed few or no immature erythropoietic elements. Erythropoiesis at this stage was normal as evidenced by the restoration of the normal ratio of leukopoiesis to erythropoiesis 100:18, as shown in table 4.

TABLE IV

Erythropoietic Elements:

(per 100 white blood cell elements)

Megaloblasts.....	1.2
Erythroblasts.....	4.6
Normoblasts.....	12.5

Changes in the leukopoietic elements of the bone marrow in active primary pernicious anemia are insignificant. Although peripheral counts show a slight decrease of the total white cells with a shift to the right, evidenced by hypersegmentation of the nuclei of the neutrophils, very little significant change from the normal was found in bone marrow granulopoiesis in this study. Some have reported alterations in the megakaryocytes. This we were unable to confirm. The failure of maturation of the red blood cell elements in this type of anemia was well shown by the megaloblastic marrow in the patients in relapse, and by the transition from this stage to a normoblastic marrow as specific therapy was instituted. This change was best studied by serial sternal punctures which may reveal progress or failure in treatment more adequately and earlier than any other method.

Macrocytic or Hyperchromatic Anemia of Pregnancy. One such case was studied. This was a white female in her seventh month of gestation. Her peripheral blood count showed 38 per cent hemoglobin (Sahli), 1,500,000 red blood cells per cu. mm. and 0.9 per cent reticulocytes. Her course in the hospital differed in no way from that of patients with primary pernicious anemia. On liver therapy she showed a reticulocyte response of 22 per cent within five days, and within several weeks her peripheral count reached 80 per cent hemoglobin (Sahli) with 4,000,000 red blood cells per cu. mm. and a normal reticulocyte count. Her bone marrow before, during and after treatment resembled in all respects that seen in pernicious anemia in its corresponding phases.

Data concerning bone marrow findings in other hyperchromatic or macrocytic anemias are scanty. However, some observers, particularly Rohr

(cited by Scott¹), report the findings in sprue to be indistinguishable from that of pernicious anemia.

Iron Deficiency Anemias. There were five patients with the idiopathic hypochromic achlorhydric variety of anemia. All were middle-aged women. In two cases there was a history of a slow blood loss over many years due to menorrhagia. In the others there was no history of blood loss. In the marrow leukopoiesis showed no significant deviations from the normal. However, the erythropoietic tissues showed a hyperplastic active marrow, the activity being proportional to the degree of anemia. There was an increase in normoblasts and erythroblasts during the anemic phase and a return to normal during treatment. One such patient with 40 per cent hemoglobin (Sahli) and 3,000,000 red blood cells per cu. mm. peripherally showed in her marrow before treatment the following: 1 megaloblast, 8 erythroblasts, and 18 normoblasts per 100 white blood cells counted, or a ratio of leukopoietic: erythropoietic elements of 100:27 instead of the average normal ratio of 100:15. As the anemia was corrected with iron therapy, the ratio as well as both the peripheral and bone marrow pictures returned to normal.

Anemia Due to Hemorrhage. In this group of cases the marrow changes apparently depended on the degree and the rapidity of the blood loss. In slow hemorrhage the bone marrow findings were similar to those found in the cases of iron deficiency anemias, namely, a hyperplastic marrow due principally to increased activity of the erythropoietic series with little or no leukopoietic changes. In those cases in which the blood loss had been great and rapid, in addition to a hyperactive erythropoietic marrow there was also observed some activity of the myeloid elements. This may account for the leukocytosis seen peripherally following this type of blood loss.

There were five such cases, two of extensive hemorrhages from bleeding peptic ulcers, two due to hemorrhage from the uterus, and one from hematemesis due to cirrhosis of the liver. The following case will be illustrative of this group. A young female with marked and severe uterine bleeding with a peripheral blood count of 39 per cent hemoglobin (Sahli), 2,200,000 red blood cells per cu. mm., and a slight leukocytosis, showed in her bone marrow smear: 2 megaloblasts, 21 erythroblasts, and 56 normoblasts per 100 white blood cells counted, a leukopoietic: erythropoietic ratio of 100:79. This returned to normal following treatment with blood transfusions, iron, and liver therapy. The marrow white cell elements showed a significant shift to the left, a finding absent in cases of slow hemorrhage.

Anemia of Thrombocytopenic Purpura. The anemia in this condition appears to be due to a non-specific blood loss. The marrow findings are similar to those in other cases of sudden great blood loss. We had one such patient, a young female, 13 years of age, with 38 per cent hemoglobin (Sahli), 2,000,000 red blood cells per cu. mm., 80,000 platelets in the peripheral blood, bleeding time of two hours with no clot retraction after 24 hours. Her marrow findings were the same as those of acute hemorrhage, namely, hyperplastic cellular erythropoietic elements with a slight increase in the

leukopoietic elements. She showed 4 megaloblasts, 15 erythroblasts, and 25 normoblasts per 100 white cells counted, a ratio of leukopoietic: erythropoietic elements of 100:44. Cure was effected by splenectomy. Within two weeks her peripheral count and bone marrow findings were both normal.

It is of interest that some stress the significance of changes in the megakaryocytes in the marrow in essential thrombocytopenia. Splenectomy is considered by these workers to be curative if a normal number of megakaryocytes is present in the marrow, and to be of no value if megakaryocytes are markedly decreased or absent. Purpuras without marrow megakaryocytes are considered phases of aplasia of the marrow in which the platelet forming progenitors are not being formed, whereas if purpura exists and megakaryocytes are present in the marrow the lack of platelets in the peripheral blood is considered to be due to an inhibiting toxic substance elaborated in the spleen. Hence splenectomy is valuable in the one instance and useless in the other. Our patient had a normal number of megakaryocytes in her marrow and she responded promptly to splenectomy.

Anemia in Carcinoma. In these cases the bone marrow findings reflect largely the presence or absence of acute blood loss. There were eight cases of anemia associated with carcinoma, the peripheral counts ranging from 34 to 70 per cent hemoglobin (Sahli) with 1,800,000 to 3,500,000 red blood cells per cu. mm. The anemias were all of the normocytic type. Five of the eight cases had definite evidence of acute blood loss, either by melena, hematemesis, or hemoptysis. In these five cases the peripheral red blood cell counts were, as a rule, lower than in the others. Total marrow counts in them ranged from 65,000 to 170,000 nucleated cells, the erythropoietic elements showed definite increased normoblastic activity, and even the myeloid elements shared in the hyperplastic activity. These findings were the same as encountered in cases of sudden hemorrhage. In the three cases with no evidence of blood loss in which cachexia was a prominent feature, the bone marrows showed few qualitative changes from the normal. However, cellularity was definitely decreased. On this basis the bone marrow could be considered depressed probably as the result of some toxic factor associated with the carcinomatous process. The marrow counts in these three cases ranged between 19,000 and 28,000 nucleated cells. This diminished cellularity was shared alike by the erythropoietic and leukopoietic elements.

Anemia Due to Sulfanilamide. There were two cases of hemolytic anemia due to sulfanilamide. In one jaundice appeared suddenly in a patient taking sulfanilamide, accompanied by a fall in the blood to 48 per cent hemoglobin (Sahli) with 2,300,000 red blood cells per cu. mm., 24,000 leukocytes with 93 per cent neutrophils, a reticulocyte count of 19.5 per cent, an icterus index of 63, and the presence of increased quantities of urobilinogen in the urine. The marrow findings in these two cases were similar, marked by a hyperplasia of all cellular elements more prominent in the erythropoietic series. There were 5 megaloblasts, 45 erythroblasts, and 72 normoblasts per 100 white blood cells, a leukopoietic: erythropoietic ratio of

100:122. These results are similar to those reported in hemolytic anemias due to other causes.

We have also studied another case of hemolytic anemia which developed in a patient with polycythemia vera from phenylhydrazine hydrochloride intoxication. On admission to the hospital he was jaundiced, and his peripheral blood count showed 66 per cent hemoglobin (Sahli) with 3,190,000 red blood cells per cu. mm. His marrow findings indicated increased cellularity, active erythropoiesis at the normoblastic stage as in the previously described sulfanilamide hemolytic anemias, and a shift to the left of the myeloid elements.

There was one case of anemia resulting apparently from toxic doses of sulfanilamide but unaccompanied by hemolysis. Here, too, the marrow findings were hyperplastic and normoblastic.

Anemias Due to Infection. A few cases of infections were studied. In general these showed findings of no positive significance. Two cases of active atrophic arthritis in the acute stage showed little change from the normal. Two cases of acute glomerular-nephritis, one with uremia, showed unimportant changes. One case of active tuberculous adenitis with septicemia showed on repeated studies little change from the normal. One case of staphylococcic septicemia, aside from a slight shift to the left of the granulopoietic series, showed no other qualitative changes. Three cases of syphilis in latent stages showed no changes. Two cases of brucellosis showed nothing characteristic in the marrow.

Aplastic Anemia. We studied three such cases. From one no bone marrow could be obtained on puncture, and the condition was proved later to be an instance of sclerotic acellular marrow. The second case showed a marked acellularity on smear and count, and an absence of young forms of the erythropoietic series. In the third instance, a case of marble bone (Albers-Schoenberg's disease), the puncture yielded no marrow.

Chronic Benzol Poisoning. One such case had gone through a severe anemia simulating the aplastic type due to exposure to benzol in his occupation. At the time of examination his peripheral blood count had almost returned to normal, showing 74 per cent hemoglobin (Sahli), 3,700,000 red blood cells per cu. mm., and 7800 leukocytes with a differential of 34 per cent neutrophils and 66 per cent lymphocytes. The bone marrow showed nothing significant.

Cooley's Anemia. A case of erythroblastic anemia in a six month old child showed a peripheral blood picture of 40 per cent hemoglobin (Sahli), 2,200,000 red blood cells per cu. mm., 13,000 leukocytes, with a normal differential, and 8800 nucleated red blood cells. The marrow reflected the erythroblastosis, the erythropoietic elements showing 10 megaloblasts, 47 erythroblasts, and 151 normoblasts per 100 white blood cells counted. The myeloid elements showed "the stimulating effect" by a shift to the left. The leukopoietic: erythropoietic ratio was 100:208.

Polycythemia Vera. Six cases were studied, four before treatment with

phenylhydrazine hydrochloride. These four showed hemoglobin levels ranging from 140 to 180 per cent (Sahli), and from 7,400,000 to 9,000,000 red blood cells per cu. mm. Two were studied after treatment with phenylhydrazine hydrochloride which had restored the peripheral blood counts to normal values. The marrow puncture findings evidenced a moderately increased activity among the erythropoietic elements, normoblastic in type. These findings were little altered after treatment. The values were: 2.9 megaloblasts, 8.5 erythroblasts and 25.5 normoblasts per 100 white blood cells counted, a leukopoietic: erythropoietic ratio of 100:37, a definite increase above normal. The lack of change after phenylhydrazine therapy may be taken as evidence that this hemolytic substance acts on the red blood cell mass in the periphery and not in the bone marrow. The granulopoietic cells showed no significant changes.

Conflicting reports on the marrow changes in polycythemia vera appear in the literature. Some have found no change even in the erythropoietic elements, whereas others have observed even greater normoblastosis in the marrow than our findings indicate.

Splenic Anemia. Three cases were so classified, cases of anemia of varying degrees with hepato-splenomegaly not conforming to any other recognized entity. In all, bone marrow studies showed no characteristic appearances.

Leukemia. In leukemia the marrow yields characteristic changes. In the diagnosis of this group of diseases marrow findings are most important. Especially is this true in what is termed "aleukemic" leukemia, a phase or species of leukemia in which the peripheral blood counts may be normal or inconclusive. In such instances the marrow usually reveals the existing state. In acute leukemia the marrow may yield diagnostic findings before characteristic peripheral blood appearances are obtainable. In chronic leukemia the marrow is usually confirmatory and corroborates the changes in the peripheral blood. In acute or leukopenic leukemia the bone marrow may be overrun with a large number of "blast" cells. In the presence of the non-specific triad of leukopenia, thrombopenia, and anemia in the peripheral blood as often encountered in Banti's disease, pernicious anemia, essential thrombocytopenia, etc., sternal puncture aspiration may on occasions reveal the diagnostic findings of leukemia.

We have studied for orientation five cases of chronic myelogenous leukemia, all of which were previously diagnosed by peripheral blood examinations. All were confirmed by bone marrow studies. One of this group, a 78 year old male, was admitted to the hospital for rectal bleeding, anemia, and splenomegaly. The peripheral count showed a total of 170,000 white blood cells with 1 per cent myeloblasts, 1 per cent promyelocytes, 25 per cent myelocytes, 10 per cent metamyelocytes, 15 per cent non-segmented neutrophils, 30 per cent segmented neutrophils, 4 per cent basophiles, 1 per cent lymphocytes, 8 per cent eosinophiles, and 5 per cent eosinophilic myelocytes. Sternal marrow aspiration showed 330,000 nucleated cells with 4

per cent myeloblasts, 7 per cent promyelocytes, 26 per cent myelocytes, 17 per cent metamyelocytes, 18 per cent non-segmented neutrophils, 18 per cent segmented neutrophils, 4 per cent eosinophils, 4 per cent eosinophilic myelocytes, 1 per cent basophils, and 1 per cent lymphocytes. The red blood cell elements in the marrow were impoverished showing 0 megaloblasts, 0 erythroblasts, and 1 normoblast. The marrow findings in this case are typical of the others and correspond with the findings described by other workers. These findings consist of an increase of the total number of the white cell series crowding the bone marrow, and increase of the primitive and young forms of the myeloid series and a decrease of the erythropoietic elements.

In four cases of chronic lymphatic leukemia selected for study in which the diagnosis had been made by peripheral blood study, the bone marrow aspirations were confirmatory. One case will be illustrative of the group. A 40 year old female was admitted to the hospital for anemia, weakness and generalized lymphadenopathy. The peripheral blood count showed 230,000 leukocytes of which approximately 100 per cent were lymphocytes. The bone marrow aspiration yielded a total count of 280,000 nucleated cells with 100 per cent lymphocytes, some of which were lymphoblasts. There were scarcely any erythropoietic elements in the marrow smear.

In "aleukemic" leukemia bone marrow study finds its greatest usefulness. We studied five cases of acute leukemia of which four were leukopenic or "aleukemic." In these latter four the diagnosis was made by bone marrow study.

Case 1. S. F., male, 46 years of age, was admitted to the hospital for marked anemia, intermittent fever, chills, and an enlarged spleen of several weeks' duration. A peripheral blood count showed hemoglobin 38 per cent (Sahli), 1,500,000 red blood cells per cu. mm., 4500 leukocytes with 54 per cent neutrophils and 46 per cent lymphocytes. The clinical diagnoses considered included: primary pernicious anemia, gastric carcinoma, typhoid fever, miliary tuberculosis, malaria, and acute bacterial endocarditis. In spite of all therapy he became worse. Two weeks later a sternal bone marrow aspiration showed a total count of 19,000 nucleated cells, with 40 per cent myeloblasts, 6 per cent promyelocytes, 16 per cent myelocytes, 9 per cent metamyelocytes, 9 per cent non-segmented neutrophils, 3 per cent segmented neutrophils, and 17 per cent lymphocytes. A definite diagnosis of acute myelogenous leukemia was thus established. The patient died after a few months, and the diagnosis was confirmed at autopsy.

Case 2. R. R., female, 13 years of age, was admitted to the hospital with a diagnosis of pneumonia because of chills, fever of 104° F., and anemia of acute onset. The hemoglobin was 36 per cent (Sahli), 1,400,000 red blood cells per cu. mm., 1900 white blood cells with 22 per cent neutrophils and 78 per cent lymphocytes. Although leukemia was suspected no bone marrow puncture was done on this admission. She made a complete recovery clinically and hematologically on transfusions, and was discharged within four weeks with a peripheral blood count of 90 per cent hemoglobin (Sahli), 4,500,000 red blood cells per cu. mm., 8500 leukocytes with 47 per cent neutrophils and 53 per cent lymphocytes. One month later she was readmitted with fever and weakness. The peripheral blood count was now 86 per cent hemoglobin (Sahli), 4,500,000 red blood cells per cu. mm., 9000 leukocytes with 46 per cent neu-

trophiles and 54 per cent lymphocytes. A bone marrow puncture at this time showed a total of 75,400 nucleated cells with 93 per cent "blasts." A definite diagnosis of acute leukopenic leukemia was thus established. The patient died within a few months and the diagnosis was confirmed at postmortem examination.

Case 3. B. C., female, 55 years of age, was admitted to the hospital for weakness, fever, weight loss, anemia and lymphadenopathy. Her peripheral blood count showed 1500 leukocytes with 50 per cent neutrophiles, 38 per cent lymphocytes, 3 per cent monocytes, and 9 per cent "blasts." Sternal puncture showed 15,500 nucleated cells of which 60 per cent were "blasts," probably monoblasts. The erythropoietic elements were strikingly diminished showing: 0 megaloblasts, 1 erythroblast, and 1 normoblast per 100 white blood cells. A diagnosis of acute leukemia was made. Later developments during life made the diagnosis of acute monoblastic leukemia possible, and this was proved at postmortem examination three months later.

Case 4. R. R., female, 60 years of age, was admitted to the hospital for ulceration of the gums and anemia. Her peripheral blood count showed 42 per cent hemoglobin (Sahli), 3,400,000 red blood cells per cu. mm., 1600 leukocytes with 15 per cent neutrophiles, 58 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophiles, 3 per cent basophiles, and 22 per cent atypical lymphocytes. Diagnoses of leukemia or primary pernicious anemia were considered. Bone marrow aspiration showed a total count of 42,000 nucleated cells with 71 per cent lymphoblasts, confirming the diagnosis of acute lymphatic leukemia. The erythropoietic elements were markedly decreased in the bone marrow.

Case 5. A. E., male, 15 years of age, was admitted to the hospital with fever of septic type, anemia, splenomegaly and lymphadenopathy. The peripheral count showed an anemia with a total leukocyte count of 45,000 of which 24 per cent were myeloblasts, 40 per cent promyelocytes, 10 per cent myelocytes, 8 per cent segmented neutrophiles, 5 per cent lymphocytes, 3 per cent monocytes, 9 per cent eosinophiles, and 1 per cent eosinophilic myelocytes. The sternal marrow confirmed the peripheral findings of acute leukemia. It showed a total count of 130,000 nucleated cells of which 63 per cent were myeloblasts, 3 per cent promyelocytes, 4 per cent myelocytes, 8 per cent metamyelocytes, 14 per cent neutrophiles, 6 per cent eosinophiles, 2 per cent lymphocytes, and a marked diminution of the erythropoietic elements.

These case reports indicate that marrow studies in acute leukemia will often disclose the condition long before it is reflected in the peripheral blood. In such cases the marrow is almost entirely replaced by "blast" cells. There is also a poverty of the erythropoietic elements, the result of either a crowding out of erythropoietic tissue or a depression of erythrocytogenesis. These cases also illustrate the difficulties of diagnosis in situations wherein anemia, fever, and leukopenia are present, and the invaluable aid bone marrow study can furnish.

Another case of leukemia worthy of mention was that of a 51-year-old female with chronic myelogenous leukemia receiving roentgen-ray therapy. On one occasion she was readmitted to the hospital for a severe attack of herpes zoster, at which time the peripheral blood count as a result of recent irradiation appeared essentially normal. A sternal puncture, however, showed a characteristic leukemic marrow well illustrating the point made by other workers⁶ that in cases of leukemia treated with roentgen-ray the bone marrow findings may be identical with untreated cases although the peripheral count may be normal.

Infectious Mononucleosis. This disease, with its acute febrile onset, glandular enlargement, frequent splenomegaly, and leukocytosis with lymphocytosis may present a trying situation to the clinician until he is able to differentiate between it, a relatively harmless self-limited disease, and the hopeless state of acute leukemia. The heterophile antibody test appears to be of value in only about 50 per cent of cases. Any rapid dependable method of differentiating between these two diseases becomes a boon to clinical medicine, by permitting safe grounds for prognosis. The bone marrow study offers such a method.

In infectious mononucleosis the bone marrow yields no characteristic findings, but the presentation of essentially normal findings despite the great increase of leukocytes and lymphocytes in the peripheral blood definitely eliminates the diagnosis of leukemia. Since the lymphocytes in the peripheral blood in this disease are atypical, the bone marrow should be examined in all such cases.

We studied 11 cases of acute infectious mononucleosis. The peripheral counts ranged from 6,000 to 20,000 leukocytes with differential counts showing as high as 94 per cent lymphocytes. The marrow counts lay within normal ranges both for leukopoietic and erythropoietic elements. The average was as follows: Total counts from 20,000 to 170,000 nucleated cells. Differential count: 1 per cent myeloblasts, 2 per cent promyelocytes, 17 per cent myelocytes, 25 per cent metamyelocytes, 36 per cent neutrophils, 13.7 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophils, and 0.3 per cent reticulum cells; and 1 megaloblast, 5 erythroblasts, and 12 normoblasts per 100 white blood cells.

Thus, the finding of a normal bone marrow when infectious mononucleosis is suspected is sufficient to eliminate the possibility of leukemia. A hopeful prognosis may, therefore, be offered. The following case will illustrate this point. A.K., male, aged six years, was admitted to the hospital with fever, glandular enlargement, and splenomegaly of acute onset. The peripheral count showed 88 per cent hemoglobin (Sahli), 4,400,000 red blood cells per cu. mm., 12,500 leukocytes with 18 per cent neutrophils and 82 per cent lymphocytes. The clinical diagnosis rested between acute lymphatic leukemia and infectious mononucleosis. The sternal marrow showed 90,000 nucleated cells with 1 per cent myeloblasts, 2 per cent promyelocytes, 8 per cent myelocytes, 12 per cent metamyelocytes, 17 per cent non-segmented neutrophils, 50 per cent segmented neutrophils, and 10 per cent lymphocytes. The erythropoietic elements were present in normal numbers. The diagnosis of a normal active marrow eliminated the possibility of acute leukemia. The child made an uneventful recovery within three weeks.

Amidopyrine Granulopenia. An excellent example of the occasional effect of amidopyrine on the bone marrow in arresting maturation of the myeloid cell elements was furnished by the following case. N.G., female,

58 years of age, was admitted to the hospital because of painful joints. Her peripheral blood count showed 92 per cent hemoglobin (Sahli), 4,600,000 red blood cells per cu. mm., 6100 leukocytes with 70 per cent mature neutrophiles. During the course of hospitalization she was given one dose of 5 grains of amidopyrine for headache. The following morning she was prostrated, apathetic, and a peripheral leukocyte count showed 3200 white blood cells with 16 per cent mature neutrophiles. A bone marrow puncture at this time revealed a general decrease of the total white blood cells with failure of maturation, showing arrest in development at the myelocytic and metamyelocytic stages as follows: Total count 17,200 nucleated cells with 1 per cent myeloblasts, 2 per cent promyelocytes, 51 per cent myelocytes, 21 per cent metamyelocytes, 15 per cent non-segmented neutrophiles, 3 per cent segmented neutrophiles, and 7 per cent lymphocytes. Erythrocytogenesis was normal, showing the selectivity of the action of amidopyrine on the myeloid cells. Ten days later the bone marrow and peripheral blood counts were both normal.

Multiple Myelomata. In this disease the marrow findings are diagnostic, as shown by the following example. R.L., female, 30 years of age, had three admissions to the hospital within one year for severe anemia, hepatosplenomegaly, and ascites. Peripheral blood count was 35 per cent hemoglobin (Sahli), 1,600,000 red blood cells per cu. mm., with a normal white blood cell count and differential. On one occasion splenectomy was performed because of suspected Banti's disease. Later tuberculous peritonitis was diagnosed. With the roentgen-ray appearance of a few rarefied areas in the skull a diagnosis of multiple myelomata was considered and a sternal marrow puncture done. This showed 180,000 nucleated cells with 82 per cent myelomatous cells confirming the diagnosis. This was further proved at autopsy some months later.

Hodgkin's Disease. Three cases were studied. No characteristic changes were observed in the marrow. Other investigators have been able to make a diagnosis from marrow studies when bone involvement is present, by the finding of the Sternberg-Reed cells.

Trichinosis. Three cases were studied. All had eosinophilia, ranging from 22 to 66 per cent. All showed marked infiltration of the mature adult eosinophile in the marrow.

Malignancy. The marrow findings in carcinoma were discussed earlier in this paper. In sarcoma we found nothing characteristic in the marrow puncture. Some investigators have been able to diagnose the presence of malignancy by the chance finding of malignant cells in the marrow aspiration.

Negative Marrow Findings as an Aid in Diagnosis. This consisted of a group of miscellaneous cases with non-characteristic involvement of the reticulo-endothelial system, showing glandular enlargements, splenomegaly, variations from the normal in the peripheral blood counts such as anemia,

tions blood dyscrasias must be considered or eliminated before the correct diagnosis can be made.

There were 60 such cases. In all, the finding of normal marrow was indispensable in the elimination of diagnoses of specific blood dyscrasias. Several such patients are presented here for illustration.

Case 1. A. R., male, 47 years of age, was admitted to the hospital because of sepsis, temperature ranging to 104° F. daily, anemia, and an enlarged hard spleen of a few weeks' duration. The peripheral blood count showed 46 per cent hemoglobin (Sahli), 2,200,000 red blood cells per cu. mm., 10,200 leukocytes with 75 per cent neutrophils, 24 per cent lymphocytes, and 1 per cent monocytes. Roentgen-ray of the chest showed some enlarged hilar glands. The clinical diagnoses considered were: "Aleukemic" leukemia, Hodgkin's disease, typhoid fever, and subacute bacterial endocarditis. A normal bone marrow study eliminated the diagnosis of leukemia. Histologic study of a gland revealed Hodgkin's disease. At postmortem examination several months later the latter diagnosis was confirmed.

Case 2. D. G., 60 years of age, was admitted to the hospital because of weakness, weight loss, generalized lymphadenopathy, and hepato-splenomegaly. No anemia was present, but the peripheral leukocytes ranged from 14,000 to 23,000 with 61 per cent lymphocytes. The diagnoses considered were lymphatic leukemia or carcinomatosis. The bone marrow puncture findings were normal. Subsequent clinical developments established a diagnosis of carcinoma. At postmortem examination carcinoma of the liver was found.

Case 3. H. L., female, 33 years of age, was admitted to the hospital because of fever, splenomegaly, anemia, and leukopenia. She had been treated in another hospital for pernicious anemia without benefit. She was suspected of having "aleukemic" leukemia but normal bone marrow findings discarded such a diagnosis. After a downhill course she died, and postmortem examination revealed carcinoma of the ovaries.

Case 4. J. B., female, 48 years of age, was admitted to the hospital because of dyspnea, ascites, anasarca, anemia and hepatomegaly. Portal cirrhosis, carcinomatosis, nephrosis, Hodgkin's disease, amyloidosis, and some form of blood dyscrasia were considered diagnostic possibilities. The peripheral blood count showed anemia and leukopenia. Normal bone marrow study eliminated a diagnosis of leukemia. At postmortem examination diffuse obliterative constrictive pericarditis was found.

Case 5. L. D., 48 years of age, was admitted to the hospital for pain in the left thigh which on roentgen-ray examination disclosed an osteolytic lesion suspected of being sarcoma, carcinoma, myeloma, or tuberculosis. Sternal puncture eliminated the diagnosis of multiple myeloma. Subsequent developments established a diagnosis of hypernephroma with metastasis to the femur.

Case 6. J. B., 50 years of age, was suspected of having multiple myeloma because of the roentgen-ray presence of rarefied areas in the humerus. Sternal puncture examination was negative for myeloma cells. Subsequent developments showed the case to be one of metastatic carcinoma.

Case 7. B. R., 27 years of age, was admitted to the hospital for weakness, anemia, lymphocytosis, splenomegaly and joint pains. Leukemia was suspected but eliminated by normal bone marrow findings. Later developments established a diagnosis of rheumatic fever.

Case 8. A. G., 58 years of age, male, was admitted to the hospital because of a disturbance in gait and pain in the lower back. Roentgen-ray examination disclosed an osteolytic lesion of the lumbar vertebrae with metastatic lesions of the pelvic bones. Carcinoma and multiple myeloma were considered in diagnosis. Bone marrow study

DISCUSSION

The value of any diagnostic procedure must be judged by the ease of its performance, its safety and the information it provides. Such considerations may outweigh absolute superiority of material. It is true that sternal biopsy provides a specimen more properly bone marrow than a marrow puncture, in that the former retains the architectural framework of the tissue and the unaltered relationship of its constituent parts. However, this procedure is a surgical one and has not for this reason been widely used. The tissue obtained requires the usual histologic treatment, involving delay in reporting and a special staining technic of some delicacy not constantly successful except in expert hands. In the majority of instances sternal puncture provides as much diagnostic information as the biopsy, since in most instances diagnosis can dependably be based on the types and relative percentage of cells observed in the smear. The staining of the smear is, moreover, as simple as that used in the ordinary differential count and is done as quickly. The cells in the marrow corresponding to those usually seen in the peripheral blood stain in the same manner and retain the same characteristics as those in the peripheral blood, and hence are easily recognized. Unusual cells have readily observable and reproducible characteristics.

In the few instances in which no adequate bone marrow can be obtained by puncture, biopsy should be resorted to. This may be necessary in cases of aplastic anemia with fibrotic or sclerotic marrows or in cases of marble bone disease in which no marrow is obtainable because of the nature of the underlying pathologic process.

We would like to stress that the great bulk of the cases presented represented problem cases in which the clinician sought aid from the procedure he ordered. Relatively few represent material obtained for study and preliminary orientation.

It will be seen from the data presented that the marrow puncture has great value in many conditions in both a positive and negative sense. It is virtually diagnostic in acute leukemia, "aleukemic" leukemia, and multiple myeloma. This also applies for leishmaniasis, malaria and Gaucher's disease. It is confirmatory in chronic leukemia in all its phases. In pernicious anemia it may help establish the nature of an obscure anemia, and will prove of great value in showing the potentialities of the bone marrow in respect to erythropoiesis and in evaluating therapy. In regard to potentialities we have found the marrow findings of value in estimating the reactive capacity of the bone marrow, particularly in anemias due to hemorrhage, and have on a few occasions been able to advise against transfusion because the marrow was hyperplastic and appeared inherently capable of generating sufficient cells to overcome an existing anemia unaided.

Bone marrow puncture is of inestimable value in a negative sense in a great host of conditions mimicking blood dyscrasias where the elimination of a specific blood dyscrasia is a matter of great import. Especially is this

true in infectious mononucleosis in which puncture enables one to offer a reassuring diagnosis and prognosis.

It should be stressed that in general the marrow findings, despite their specific character in certain diseases, should be regarded and evaluated as an additional finding, set in a general clinical composite. The bone marrow, like other tissues of the body, reflects the effects of pathologic processes elsewhere in the body and, because of the naturally limited varieties of response of which tissues are capable, may on occasions be the seat of changes approximating in degree or kind the abnormal specific changes representative of the true blood dyscrasias. That possibility should be no more confusing than similar difficulties in evaluating data in other diagnostic fields in which similar circumstances have arisen.

CONCLUSIONS

1. Bone marrow puncture is a simple, adequate and safe method of studying the living marrow. It is usable at all age periods and in all disease processes.

2. Bone marrow puncture is of inestimable value in the diagnosis and prognosis of diseases of the blood-forming organs.

3. It is of especial importance in excluding diseases of the blood-forming organs as a diagnostic possibility in many obscure conditions.

4. It provides material for an appraisal of the potentialities of the bone marrow.

5. It should, therefore, be considered as an essential adjunct in the study of any hematologic problem.

6. A series of 300 sternal punctures performed on nearly as many patients over a period of three years, chiefly in diagnostically uncertain cases, is presented to illustrate the above principles.

BIBLIOGRAPHY

1. SCOTT, R. B.: Sternal puncture in diagnosis of diseases of blood forming organs, *Quart. Jr. Med.*, 1939, viii, 127.
2. NEUMANN, E.: Über die Bedeutung des Knochenmarkes für die Blutbildung, *Centralbl. f. d. med. Wissensch.*, 1868, vi, 689.
3. NEUMANN, E.: Über die Bedeutung des Knochenmarkes für die Blutbildung, *Arch. der Heilkunde*, 1869, x, 68.
4. GHEDINI, G.: Per la patogenesi e per la diagnosi delle malattie del sangue e degli organi emopoietici, puntura esplorativa del midollo osseo, *Clin. med. ital.*, Milano, 1908, xlvii, 724.
5. SEYFARTH, C.: Die Sternumtrepanation, eine einfache Methode zur diagnostischen Entnahme von Knochenmark bei Lebenden, *Deutsch. med. Wchnschr.*, 1923, xlix, 180.
6. ARINKIN, M. I.: Methodology of examining bone marrow in living patients with hematopoietic disease, *Vestnik. khir.*, 1927, x, 57.
7. ARINKIN, M. I.: Die intravitale Untersuchungsmethodik des Knochenmarks, *Folia haemat.*, 1929, xxxviii, 233.
8. VOGEL, P., ERF, L. A., and ROSENTHAL, N.: Hematological observations on bone marrow obtained by sternal puncture, *Am. Jr. Clin. Path.*, 1937, vii, 436.
9. JAFFE, R. H.: The bone marrow, *Jr. Am. Med. Assoc.*, 1936, cvii, 124.

A PATHOLOGICAL STUDY OF THE SIGNIFICANCE OF THE SYSTOLIC MURMUR *

By M. S. REDNICK, M.D., F.A.C.P., *Ossining, New York*

THE subject of the systolic murmur is still a broad and rather unsettled phase of cardiology, and although much has been added to the general knowledge concerning the etiology and mechanics of this murmur, full progress and complete understanding in this important field have not kept pace with advances made in other branches of medicine. A search of the literature reveals a rather surprising number of divergent views which have been expressed regarding the cause, significance and interpretation of the systolic murmur.

The factors entering into the production of a murmur are well brought out by Sprague² who states "that a cardiac murmur is an audible vibration produced in the circulating blood by the formation of rhythmic eddies. These eddies are the result of a disturbance in the stream flow, produced where a region of discontinuity occurs when streams of different velocities are opposed. Such changes occur when a relatively narrow jet of fluid is projected into a vessel or chamber of wider diameter. To be audible the jet must have a velocity of a critical level and this is determined not only by the diameter of the stream but by the pressure difference behind and ahead of the constriction."

Although it is generally agreed at the present that the diastolic murmur, with rare exceptions, denotes a cardiac valvular pathologic lesion, the rôle and significance of the systolic murmur have not been fully established. The various opinions given concerning its value range from complete acceptance as a pathognomonic indication of an organic lesion to almost total disregard of it as an aid in the diagnosis of heart disease.

Auscultation, as a method in physical diagnosis, was first introduced by Laennec¹ in 1819. He revealed a surprising comprehension of heart sounds and expressed the opinion that all murmurs were positive indications of the presence of cardiac valvular lesions. Subsequently he denied these statements when he found that postmortem examination of such patients with murmurs failed in certain instances to reveal the lesions he anticipated.

In varying positions between these two opposite views expressed by Laennec range the conceptions of later workers, based on numerous clinical and experimental investigations. From these studies it became evident that the systolic murmurs were caused not only by deformities of the valves, but by other factors not clearly defined, and in some instances occurred in what seemed to be entirely normal hearts. This led to several classifications

* Received for publication January 11, 1939.

of the systolic murmur, the most familiar one dividing the cases into two categories, organic and functional.

Attempts to differentiate between organic and functional murmurs have been made repeatedly by many clinicians who have formulated criteria for that purpose.

Morse ⁴ contends that there is no certain distinction to be made between such murmurs. White ⁵ states that the louder a murmur the more likely it is to be organic.

Bass, Mond, Messeloff, and Oppenheimer ⁶ consider it of prime importance to make such differentiation and, after studying a large series of cases, found that most methods already in use were unreliable. They decided that differentiation could be accomplished best by phonocardiographic records.

Maliner ⁷ advised the use of subcutaneous injections of epinephrine for the same purpose and concluded that 71 per cent of children thought to have functional murmurs had in reality some underlying organic condition.

For a time the determination as to the presence of cardiac disease in a patient was limited in the main to a search for the presence or absence of murmurs. To emphasize the inadequacy of such methods MacKenzie ⁸ often advised throwing the stethoscope away entirely. Cabot ⁹ later wrote that the systolic murmur without the presence of other signs of heart disease was of no importance, and White remarks that most systolic murmurs do not indicate the presence of any organic heart disease. On the other hand, Levine ¹⁰ observes that a systolic murmur is not common in normal individuals and that louder ones are always associated with some form of cardiovascular disease. Further, all systolic murmurs deserve consideration, even if the patient looks well and has no symptoms or signs of cardiac insufficiency.

According to Herrick, ¹¹ two important conditions in the heart may be betrayed by a systolic murmur—a rheumatic heart and beginning sclerosis in a valve. Some of the pathological and clinical factors recognized as causing systolic murmurs of the organic type are: stenosis or insufficiency of the valves; certain congenital deformities as patent *ductus Botalli*, patent inter-ventricular septum, patent interauricular septum, muscular bands, ² anomalous *chordae tendineae* and papillary muscles; vegetations and sclerotic changes of valves. Causes of functional murmurs are: stretching of valve rings, dilatation of chambers, hypertrophy, anemia, tachycardia, fever, and neuro-circulatory asthenia. In addition to these factors Bystritsky, Zuelger, Lederer and Stolte ¹³ noted that systolic murmurs were produced in certain disorders of the myocardium and concluded that such murmurs may occur with decreased cardiac tonus and contraction. In the opinion of Zuelger ¹² a systolic murmur may be the earliest indication of cardiac weakness. Friedlander and Brown ²⁸ were able to show that not only exercise but certain drugs such as epinephrine were capable of producing a systolic murmur.

Therefore, the necessity for the early recognition of the nature of a murmur becomes at once apparent. In some instances a seemingly innocent

murmur may be owing to some remote organic change in the cardiovascular system, or it may indicate the potentialities for the subsequent development of manifest stenosis of the mitral valve,¹⁰ or be an accompaniment of hypertension or subacute bacterial endocarditis. In young people it may be the only indication that the patient has had a rheumatic infection. Robey¹⁴ cautions against the great harm that may result to a patient by making a diagnosis of cardiovascular disease on a murmur alone, and emphasizes the importance of properly evaluating a good history and other circulatory signs before the stethoscope is employed. On the other hand, many serious conditions may exist without the presence of a murmur, such as syphilitic aortitis, hypertensive heart disease, and coronary artery disease.

Fahr¹⁵ conducted a study on a series of normal children and on an older group of individuals and found that 40 to 70 per cent of all children examined between the ages of six and 14 years and 35 per cent of otherwise normal older individuals in the second decade have murmurs. He adds that if no diastolic murmur appears during the first or second year following the last attack of rheumatic fever and if the size and shape of the heart have not changed significantly, the murmur is undoubtedly of no consequence. Levine¹⁶ examined 1000 normal persons engaged in various occupations and found that 19.6 per cent of these presented a systolic murmur. In a group of university students, Reid¹⁷ found 20 per cent with a systolic murmur. In a series of experiments on dogs, Thayer and McCollum¹⁸ have shown that a systolic murmur can be produced at the pulmonary orifice by slight pressure of the stethoscope on the thin walled conus; and that bleeding and even subsequent intravenous infusion of salt solution might likewise be followed by this murmur.

It is obvious, therefore, from the above that the current clinical teaching which tends to disregard the significance of all systolic murmurs is just as unsound as the older view which associated every adventitious sound with organic disease. Somewhere between these two extremes lies the truth.

Many investigations have been carried out to substantiate these views, most of them on a clinical or experimental basis. Further investigation, from another approach, was therefore decided upon. Hence the present study was undertaken on a pathological basis, correlating the clinical observations with the subsequent pathological findings on postmortem examination.

METHOD

The records of Grasslands Hospital were examined, covering a period of five years from 1933 to 1938. The charts selected were those of all deaths in the hospital which had come to necropsy. Records which were incomplete, traumatic cases, and those patients whose stay in the hospital was not sufficient to permit of a complete physical examination and work-up were rejected. Of this group, all cases presenting a systolic murmur clinically were chosen. The final acceptance of the presence of a murmur was

carefully determined by comparing all notations and physical examinations made by the attending and house staffs. Any disagreement as to a murmur or failure to mention a murmur eliminated that chart from the study. The age, sex, history, physical findings, clinical diagnosis and postmortem examination were noted. Sub-groups were then made of etiological factors, history, valvular pathology, and other associated conditions.

The total number of cases examined in this study was 1148. Of this number, 268 or 23.1 per cent were found to have clinically one or more systolic murmurs. The apex proved the most frequent site of murmurs (222 instances). This was followed by the aortic area (61 instances), the pulmonic area (3 instances), and finally by the tricuspid area (1 instance).

Diastolic murmurs were associated with systolic murmurs 33 times. The final diagnoses in this group of 33 cases with associated diastolic murmurs included: 26 cases of valvular stenosis and insufficiency, three cases of aneurysm, and four cases of densely calcified valves.

The analysis of the records of this series of cases with systolic murmurs led to a subdivision of the cases into three groups according to the character of the findings which bore a relation to the occurrence of the murmur.

- I. Pathological findings
 - (a) valvular incompetence
 - (b) valvular deformity
 - (c) cardiac hypertrophy
- II. Clinical findings
- III. No findings

PATHOLOGICAL FINDINGS

Sub-group (a): Of the 268 cases with systolic murmur either alone or associated with a diastolic murmur, 44 cases or 16.4 per cent were found in sub-group (a), comprised of cases showing evidence of valvular stenosis and insufficiency. This group was further subdivided according to etiology as follows:

a. Rheumatic	21 cases or 47.7 per cent
b. Arteriosclerotic	14 cases or 31.8 " "
c. Syphilitic	5 cases or 11.3 " "
d. Congenital	4 cases or 9.1 " "

Total 44 cases

Cases placed in the rheumatic group had all given a history of one or more attacks of rheumatic fever at one time. The various valvular lesions occurred in the following order of frequency:

1. Mitral stenosis 21
2. Mitral insufficiency 7
3. Aortic stenosis 2
4. Aortic insufficiency 2
5. Tricuspid insufficiency 1

Mitral stenosis, therefore, occurred in all cases, either alone or in combination with other lesions. It occurred together with mitral insufficiency seven times, but mitral insufficiency never occurred alone. Aortic stenosis and aortic insufficiency also were twice noted associated with mitral stenosis, but were not observed as single lesions. Tricuspid insufficiency was seen once and then occurred in combination with mitral stenosis.

The age limits of these patients were interesting. The oldest patient in this series was 60 years old, the youngest was 4. However, one patient was 51, another 40, and five patients were in their thirties. The average age of these persons was 26.1 years. Death in all cases resulted from heart disease and this was clinically diagnosed. There were three cases of subacute bacterial endocarditis.

The *arteriosclerotic* group followed the rheumatic group as to the number of valvular lesions with 14 cases or 31.8 per cent. The order of frequency of these lesions was as follows:

1. Aortic stenosis 8
2. Mitral stenosis 6
3. Mitral insufficiency 3
4. Aortic insufficiency 2

Aortic stenosis was the most frequent valvular condition found in arteriosclerosis. It occurred with aortic insufficiency once. However, it did not occur in all cases as in the rheumatic group. Mitral stenosis was seen with mitral insufficiency occurring without aortic involvement.

All cases presented advanced clinical arteriosclerotic changes elsewhere in the body. The ages of these patients ranged from 86 for the oldest to 45 for the youngest, with an age average of 71.1 years. In this group the majority of cases, eight in number, died of arteriosclerotic heart disease, but the remaining six died of other causes which included malignancy, pyonephrosis, and fracture of the femur.

The *syphilitic* group was the third largest group with five cases. The frequency of the lesions found was:

1. Aortic insufficiency 4
2. Aortic stenosis 3
3. Mitral stenosis 1

Aortic insufficiency was the most frequent valvular condition encountered in syphilis, occurring four times. Aortic stenosis was noted three times and mitral stenosis once. The latter two did not occur alone but in combination with aortic insufficiency. The blood Wassermann was four plus positive in all cases, and in four cases there were clinical manifestations of syphilis elsewhere. The ages of these patients ranged from 77 to 32 years. The average age was 57.7 years. Death in these cases resulted in all instances from syphilitic heart disease.

The *congenital* group numbered four and represented the smallest group of cases of valvular heart disease, although it numbered only one less than the syphilitic group. These were all diagnosed as having congenital de-

fects and with one exception died as a result of the lesion. The single exception died of anemia. The frequency with which these lesions occurred was:

- | | |
|---------------------------------------|---|
| 1. Patent foramen ovale | 3 |
| 2. Patent <i>ductus Botalli</i> | 1 |

The ages of these patients were two months to four years, with an average of 1.2 years.

In the second group of pathological changes fell a large number of valvular abnormalities which were not sufficient to cause incompetence of the valve, but nevertheless revealed deformities which were sufficient to produce murmurs mechanically. These cases numbered 136 or 50.7 per cent. and the nature of these changes follows:

- | | |
|--------------------------------|----|
| 1. Sclerotic valves | 47 |
| 2. Thickened valves | 33 |
| 3. Calcified valves | 24 |
| 4. Stretched valves | 13 |
| 5. Scarred valves | 7 |
| 6. Vegetations on valves | 7 |
| 7. Nodules on valves | 5 |

Total 136 or 50.7 per cent

More than half of all murmurs, therefore, fell into this group. These individuals were, with few exceptions, elderly people, the oldest being 97, and the average age 73.4 years. Deaths resulted from arteriosclerotic heart disease and hypertensive heart disease in 37 cases, vascular accidents in 11 cases, and in the remainder from miscellaneous causes.

Aneurysm was found in four cases or 1.4 per cent. These were found in the ascending aorta and the aortic arch. They were divided as follows:

- | | |
|---------------------|---------|
| 1. Arteriosclerotic | 3 cases |
| 2. Syphilitic | 1 case |

Total 4 or 1.4 per cent

The syphilitic patient was 45 years old, whereas the arteriosclerotics were 61, 69 and 85 years old with an average of 71.6 years. Two were diagnosed before death. Of the other two cases, one was designated as vascular collapse and the other occurred undiagnosed in a patient with psychosis. Hypertrophy of the heart without any valvular abnormality was noted 25 times or in 9.3 per cent. The ages ranged from 97 to 27 with an average of 61.2 years. These comprised mainly miscellaneous cases.

There were, therefore, 209 cases or 78.2 per cent for whose murmurs some pathological explanation was found.

In the remaining 49 cases or 18.1 per cent, the examination revealed no anatomical basis for the presence of murmurs; however, the clinical history disclosed certain conditions which were known to produce murmurs. These were as follows:

1. Fever	21 cases
2. Hypertension	15
3. Anemia	10
4. Tachycardia	3

Total 49 cases or 18.1 per cent

Finally, in the remaining 10 cases or 3.7 per cent no evidence, either clinical or pathological, was found to account for the systolic murmurs.

The sexes were practically equally represented in the cases showing systolic murmurs, the males comprising 50.2 per cent and the females 49.8 per cent.

CONCLUSIONS

The present study comprises an examination of the autopsy records of 1148 consecutive cases of whom 268 cases or 23.1 per cent had manifested systolic murmurs. Only 16.4 per cent of the cases with systolic murmurs presented actual evidence of valvular incompetence. The etiologic factors in this series proved to be rheumatic fever, arteriosclerosis, syphilis and congenital malformations in the order named. It was further observed that these patients all exhibited additional signs and symptoms of cardiac involvement. Among these were precordial thrills; diastolic murmurs, blood pressure changes, cardiac enlargement and a positive serological reaction for syphilis. In the rheumatic group a history of one or more attacks of rheumatic fever was elicited. This tended to emphasize the value of a careful history and close observation for other features of valvular stenosis and insufficiency. Thus the discovery of a systolic murmur not accompanied by any of the above characteristics must be viewed with caution from a diagnostic and prognostic standpoint. Characteristic lesions were found representative of each group. They were mitral stenosis in rheumatic hearts, aortic stenosis in arteriosclerotic cases, aortic insufficiency in syphilitic cases, and patent foramen ovale in the congenital group. However, it was noteworthy that except for limitation of a patent foramen ovale to the congenital group the other lesions occurred in any of the other groups.

The largest group in this series comprised 136 cases or 50.7 per cent. These cases were found to present pathologically various types and stages of valvular deformity. Although anatomically these valves were still competent, yet physiologically they were capable of murmur production. Here were noted various stages of sclerosis of the valves: vegetations, nodules and calcification of the valve leaflets or valve ring, as well as stretched and

scarred valves. Apparently some of these conditions represent mid-stages of rheumatic involvement of the endocardium as indicated by the finding of vegetations and nodules. On the other hand the thickening, calcification and scarring appeared to represent various degrees of arteriosclerotic change, which in some manner became arrested and did not proceed quite to the production of actual valve incompetence. Hence, although the systolic murmurs in this type of case resulted from a definite pathological change in the endocardium, they were classified generally as belonging to the functional group of murmurs. It was likewise noted that these conditions were compatible with long life, the average age at death being 73.4 years, with the oldest patient 97 years.

Aneurysm and cardiac hypertrophy also represented small groups of anatomically explained murmurs.

In a group of 18.1 per cent of cases the appearance of systolic murmurs was attributed either to fever, tachycardia, anemia or hypertension. These cases were anatomically normal.

Finally, in 10 cases or 3.7 per cent no clinical or pathological explanation for these murmurs was found.

BIBLIOGRAPHY

1. VAQUEZ, L.: Diseases of the heart, 1924, W. B. Saunders & Company, Philadelphia, 69.
2. SPRAGUE, H.: Mechanism of the production of heart murmur, *Modern Concepts of Cardiovascular Disease*, 1937, vi, 9-10.
3. Nomenclature and criteria for diagnosis and diseases of the heart, 1932, N. Y. Heart Assoc., New York, 6.
4. SULLIVAN, A.: Significance of murmurs, *Tri-state Med. Jr.*, 1931, iv, 767.
5. WHITE, P.: Heart disease, 1937, The Macmillan Company, New York, 40.
6. BASS, M., MOND, H., MESSELLOFF, C., and OPPENHEIMER, E.: The systolic murmur in children, *Jr. Am. Med. Assoc.*, 1933, ci, 17.
7. MALINER, M., and OKIN, I.: The significance and a differential diagnostic test of precordial murmurs in children, *Jr. Pediat.*, 1937, x, 77.
8. MACKENZIE, J.: Oxford system of medicine, Oxford Univ. Press, New York, ii, 464.
9. CABOT, G.: Facts on the heart, 1926, W. B. Saunders & Company, Philadelphia, 293.
10. LEVINE, S.: Systolic murmur—its clinical significance, *Jr. Am. Med. Assoc.*, 1933, ci, 436.
11. HERRICK, J.: Discussion on systolic murmur, *Jr. Am. Med. Assoc.*, 1933, ci, 436.
12. ZUELGER, G.: The systolic murmur, *New York State Med. Jr.*, 1937, xxxvii, 1289.
13. ZUELGER, G.: Systolic murmur—symptomatic importance in heart muscle weakness, *New York State Med. Jr.*, 1937, xxxvii, 1289-1292.
14. ROBEY, W.: Significance and interpretation of heart murmurs in general practice, *Med. Clin. North Am.*, 1935, viii, 893.
15. FAHR, G.: Significance of the systolic murmur, *Nebraska State Med. Jr.*, 1930, xv, 458.
16. LEVINE, S.: Clinical significance of the systolic murmur, *ANN. INT. MED.*, 1933, vi, 1371.
17. REID, W.: Heart murmurs in the practice of medicine, *New England Jr. Med.*, 1937, cciv, 597.
18. THAYER, W.: Reflections on the interpretation of systolic cardiac murmurs, *Am. Jr. Med. Sci.*, 1925, clxix, 313.
19. SCOTT, R.: The systolic murmur in clinical medicine and in insurance examinations, *Ohio State Med. Jr.*, 1935, xxxvii, 943.
20. HUNTER, J.: The apical systolic murmur, *Virginia Med. Monthly*, 1936, lxiii, 303.

21. ROSENTHAL, M.: Anatomic mechanism in production of Flint murmur, *Arch. Path.*, 1933, xvi, 862.
22. NIEHAUS, F.: Apical systolic murmur and mitral regurgitation, *Nebraska Med. Jr.*, 1936, xxi, 464.
23. REIFENSTEIN, E.: The significance of cardiac murmurs, *Internat. Clin.*, 1937, iii, 159.
24. WURTZER, E.: Significance of systolic apical murmurs, *Jr. Iowa State Med. Soc.*, 1934, xxiv, 626.
25. FINEBERG, H., and STEUER, L.: Apical systolic murmurs in children, *Am. Heart Jr.*, 1934, vii, 553.
26. WOLFERTH, E.: Auriculosystolic murmur in tricuspid area during convalescence from acute coronary occlusion, *Am. Jr. Med. Sci.*, 1935, clxxxvi, 739.
27. LEECH, C.: The Austin Flint murmur and differential diagnosis, *New England Jr. Med.*, 1934, ccxi, 1007.
28. FRIEDLANDER, R., and BROWN, M.: The systolic murmur: further observations on its clinical significance, *ANN. INT. MED.*, 1935, viii, 893-899.
29. NEUHOF, S.: *The heart*, 1923, P. Blakiston's Son and Company, Philadelphia.
30. WOLFERTH, C., and MARGOLIES, A.: Various types of extra heart sounds, *Med. Clin. North Am.*, 1931, xiv, 897.
31. BERGER, S.: Significance of systolic murmurs, *Ohio State Med. Jr.*, 1927, xxiii, 569.
32. LENDON, G.: Interpretation of the systolic murmur, *Med. Jr. Australia*, 1934, i, 613-617.
33. MCCRUDDEN, F.: Murmurs and their significance, *New England Jr. Med.*, 1931, cciv, 598.
34. OKIN, I.: Non-pathologic or functional murmurs in childhood, *Jr. Med. Soc. New Jersey*, 1931, xxxviii, 100.
35. SULLIVAN, A.: Significance of murmurs, *Tri-state Med. Jr.*, 1931, iv, 767.

NEUROBLASTOMA (SYMPATHOBLASTOMA OR NEUROCYTOMA) OF THE SUPRARENAL MEDULLA; REPORT OF THREE CASES *

By RALPH M. THOMPSON,† M.D., F.A.C.P., *Hot Springs National Park, Arkansas*

THE sympathetic nervous tissue comprising the medullary portion of the suprarenal gland is the site of a relatively rare and spectacular group of tumors. In the past this subject has received some prominence in the medical literature, various writers having stated that cases are rare.

Tumors derived from the sympathetic nervous system of the suprarenal medulla may be divided into three well defined pathologic types, namely: (a) Neuroblastoma (sympathoblastoma or neurocytoma); (b) ganglioneuroma (neuroma ganglionare); (c) paraganglioma (chromaffin cell tumors). In this paper, along with the cases reported, discussion will be limited principally to the suprarenal neuroblastoma which occurs almost entirely in infants and children, and only occasionally in young adults. These cases constitute a definite pathologic entity, the clinical picture of which is quite varied and severe, as they always terminate fatally.

Virchow,¹ in 1864, was the first to study and report a case of primary malignant tumor of the suprarenal gland in children and designated it a glioma. Marchand,² in 1891 described a similar cellular tumor in an infant nine months of age and attributed the origin to the sympathetic nervous system. Kuster,³ in 1905, described a cellular neoplasm of the suprarenal gland in an infant of 14 weeks which he interpreted as neuro-epithelial in origin, and at the same time described the characteristic alveolar rosette structures which are common to some of these tumors. In the literature these neoplasms have frequently been referred to as gliomas, round cell sarcomas and lymphosarcomas. In 1910 J. H. Wright⁴ presented an excellent description of these tumors and rather definitely stated that they were of neuroblastic origin. Frew,⁵ in 1910, reported several cases of neuroblastoma, several of which he collected from the literature. These he called carcinomas of the suprarenal medulla. Wahl⁶ in 1914, Dunn⁷ in 1915, Lehman⁸ in 1917, Scott, Oliver and Oliver⁹ in 1933, Lewis and Geschickter¹⁰ in 1934, and Redman, et al.¹¹ in 1938, have contributed greatly to our present knowledge of these new growths and have added cases to the literature.

A better understanding of the neoplasms of the suprarenal medulla can best be obtained after reviewing the embryogenesis of the organ. The suprarenal gland consists of an outer cortical zone (interrenal organ) derived

* Received for publication July 23, 1940.

From the Department of Pathology, Walter Reed General Hospital, Washington, D. C.

† Lt. Colonel, Medical Corps, U. S. Army.

from the celomic epithelium, and a central medullary zone (suprarenal organ) which arises from the celiac sympathetic plexus and so is composed of sympatho-chromaffin tissue. The cortex develops earlier than the medulla, and in embryos of 9 mm. buds of cells from the celomic epithelium at the root of the mesentery become detached to form the suprarenal ridge. At 12 mm. the cortical portion is large. The medulla of the gland is formed by the primordial chromaffin cells which are termed neuroblasts or sympathogones. These cells emanate from the neural crest and migrate from

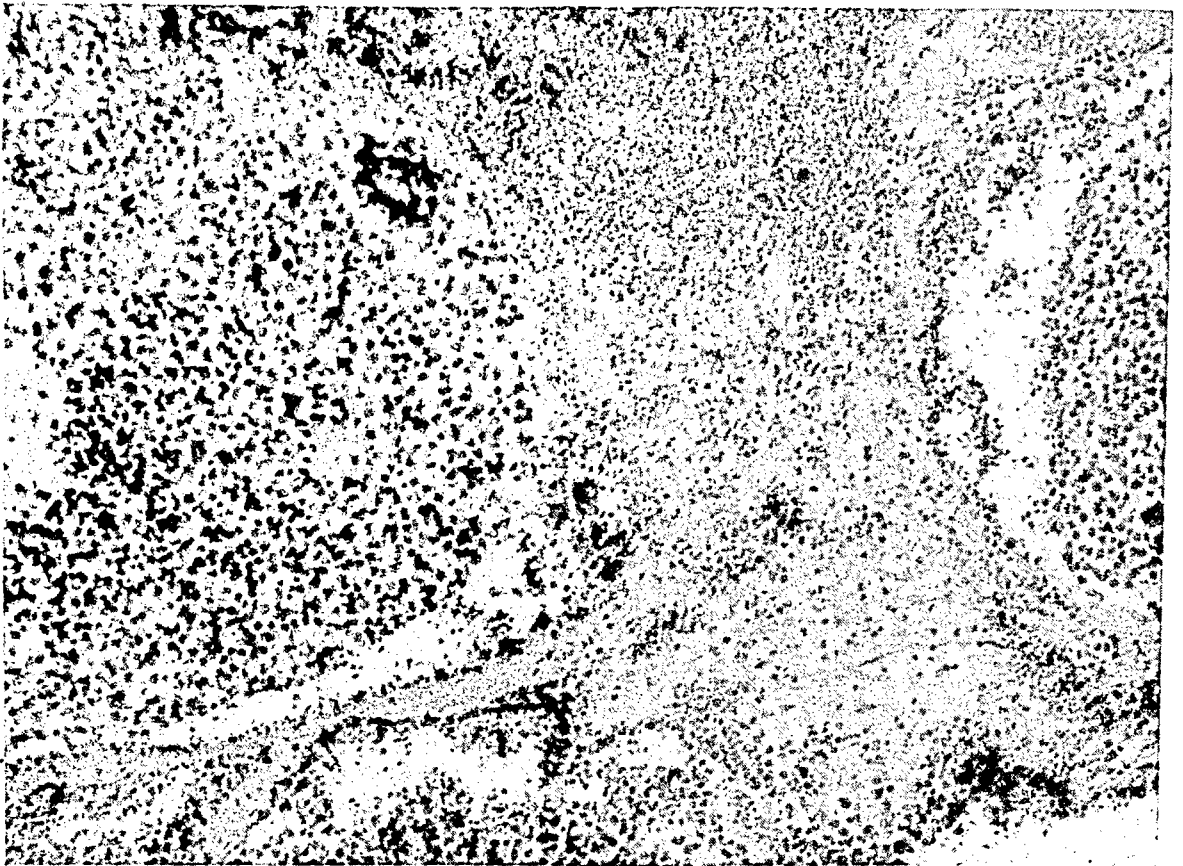


FIG. 1. *Case 1.* Microphotograph of neuroblastoma showing neurocytes, fibrillar matrix and an atypical rosette in the upper left quadrant. Hematoxylin and eosin stain. $\times 205$. (U. S. Army Medical Museum Neg. No. 68988.)

the celiac plexus to the centers of the cortical masses. This migration begins at about the 19 mm. stage and continues until after birth. During migration the cells are immature and indifferent. Later the neuroblast or sympathogone develops either into the sympathoblast (neuroblast) or the phaeochromoblast and, in the further development, the sympathoblast is the precursor of the adult sympathetic ganglion cell, whereas the phaeochromoblast becomes the parent of the phaeochromocyte. As a consequence of distinguishing these various type cells emanating from the sympathogone, we can recognize and understand better the three types of medullary supra-

renal tumors previously mentioned as well as the allied tumors of the paraganglia and carotid body whose cells are similarly derived.

Thus, it is noted that the suprarenal cortex is of mesoderm origin whereas the medulla is of ectoderm origin; also, that tumors of the undifferentiated and immature neuroblasts may well be termed neuroblastomas, whereas those made up of the more differentiated, mature cells and fibers are called ganglioneuromas, and those formed from the chromaffin cells are called paragangliomas or phaeochromocytomas.

The paragangliomas or chromaffin cell tumors occur almost entirely in the third to sixth decades of life. They are quite rare, relatively benign in character, and histologically appear quite varied. These tumors of the suprarenal are quite similar to those chromaffin cell tumors that occur in other locations, for example, the carotid body, paraganglia and gastrointestinal tract. These latter tumors are frequently called argentaffin or carcinoid tumors. Neoplasms of the chromaffin tissue of the suprarenal contain cells in various stages of differentiation. The most common element is the large polygonal cell which frequently assumes a characteristic brown granular color after fixation in chrome salts, this reaction being constant in only the mature cells. These tumors are small, often encapsulated, frequently bilateral, and are usually accidental findings at autopsy. Metastases have been described. The growth presents small masses of round, oval and polygonal cells with occasional giant cells having single or multiple nuclei. The pigment is irregular, and at times the cells show very definitely their chromaffin nature after fixation in solutions of chrome salts.

The ganglioneuromas, first described in 1881 by Weichselbaum,¹² may occur at any age but are quite rare after 40. This tumor is not so common as the neuroblastoma. It arises from well differentiated sympathetic nerve tissue, and is relatively benign in character. It may reach considerable dimensions. The histologic picture shows a preponderance of medullated and non-medullated nerve fibers in which are masses or islands of well formed ganglion cells. Fibrous tissue may be present in varying amounts according to some writers.

The neuroblastoma or neurocytoma is by far the most common of the tumors originating in the suprarenal medulla, and occurs chiefly in children and young adults. It is related to the retinoblastoma of the eye and the medulloblastoma of the cerebellum. In 1933 Scott, Oliver and Oliver,⁹ reviewed the literature and reported a total of 98 cases of sympathoblastoma (neuroblastoma) of which four were their own. In 1938 Redman, Agerty, Barthmaier and Fisher¹¹ reported finding an additional 113 cases. Since then a few other cases have been reported, bringing the total number of cases to about 220. Even with this number reported, these tumors are considered rare.

In an analysis of all cases reported the males predominated over the females in the ratio of 4 to 3, which is not highly significant. Because the

majority of cases occur in children under the age of five years, little emphasis can be placed upon other etiologic factors, such as trauma and previous afflictions.

In the literature two distinct clinical syndromes caused by this tumor are described, both of which are based upon the location of the metastatic lesions. These are termed the Pepper and Hutchinson syndromes and practically all writers attempt to classify their cases in one or the other of these, the reasons for which are not clear.

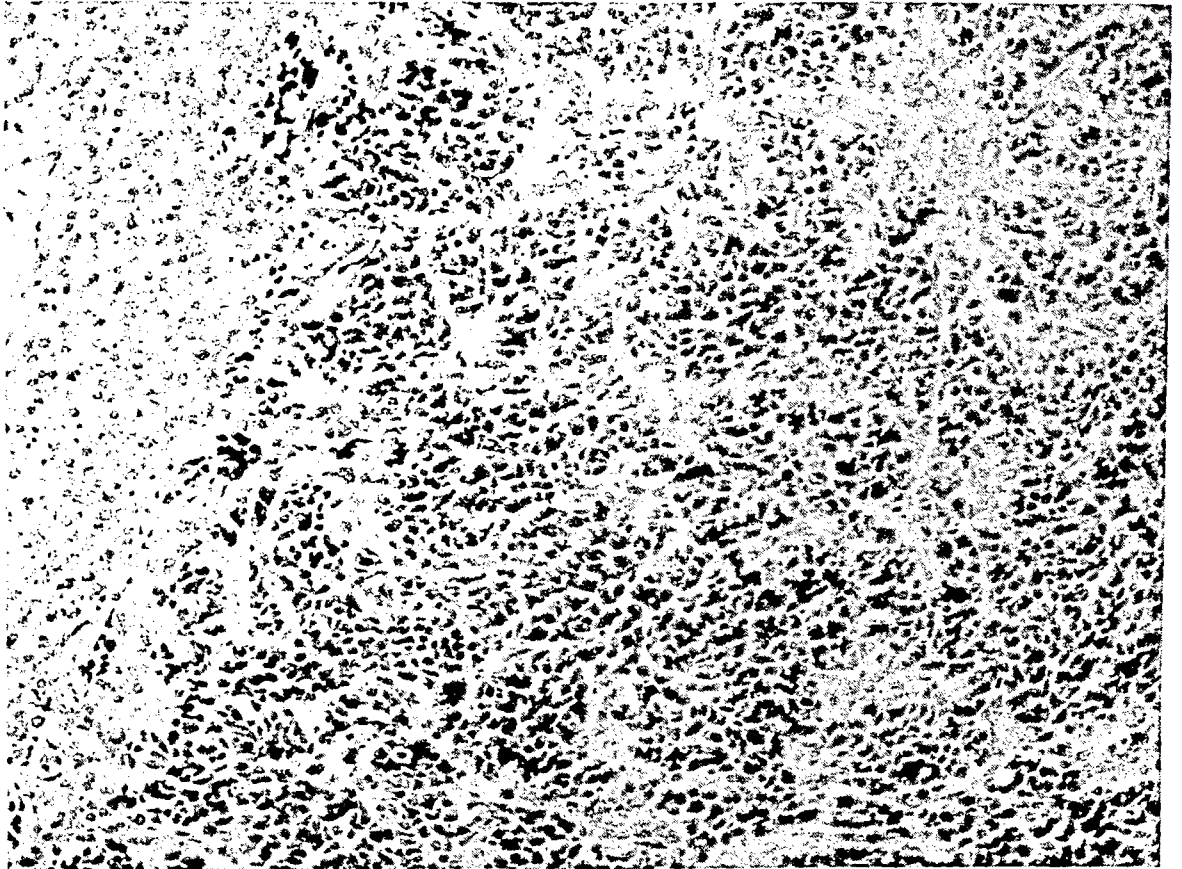


FIG. 2. *Case 2.* Microphotograph of neuroblastoma, a metastatic lesion of the liver, showing the fibrillar matrix about groups of small spindle and polygonal shaped cells with hyperchromatic nuclei. Hematoxylin and eosin stain. $\times 205$. (U. S. Army Medical Museum Neg. No. 68990.)

Pepper,¹³ in 1901, described six cases of neuroblastoma of the suprarenal medulla which he called round cell or lymphosarcoma. One of these cases was his own and the other five he collected from the literature. These six cases showed similarity in that they all occurred in females from 3 to 11 weeks of age and all showed marked liver metastases. None of these cases showed any metastases to bone. Three cases were primary in the right gland, one in the left, one was bilateral, and in one case no location was recorded. Therefore, it is suggested that a neuroblastoma of the suprarenal

gland in very young infants, occurring in one or the other organs with liver metastases only, be classified as one of the Pepper type. The liver metastases from the right suprarenal are apparently by extension.

Hutchinson,¹⁴ in 1907, described 10 cases of suprarenal "sarcoma" in children from three months to nine years of age and emphasized the fact that metastases occurred in the bones of the skull and that all cases occurred spontaneously after trauma. He noted the presence of ecchymosis of the periorbital soft tissue followed by exophthalmos, tumor of the orbital bones, and metastases to the auricular and submaxillary lymph nodes. He described a secondary anemia in all cases but failed to mention the leukocytic picture. At autopsy a suprarenal medullar tumor was found on the left side in six cases and on the right in four, the growth varying in size from that of a small walnut to that of a child's head. He also mentioned that metastases are sometimes found in the ribs, sternum and vertebrae but was doubtful as to their presence in the long bones.

From a survey of the cases reported it is believed that entirely too much emphasis has and is being placed upon these two syndromes because features of both are noted in many of the cases and also, in many, the salient features are absent. In the literature the cases which show a great deal of overlapping of various criteria are listed as "unclassified," and about 20 per cent of the cases reported fall into this category. In our second case which occurred in a male child, aged five years, the tumor was primary in the right suprarenal, extended to the liver, and showed widespread bone metastases. Our third case simulated the Pepper syndrome with the exception that it occurred in a young, adult male, aged 18 years.

Frew,⁵ in 1910, attempted to analyze the clinical pictures of both the so-called Pepper and Hutchinson syndromes by the presumed metastatic routes and stated that tumors originating in the left suprarenal gland metastasize, by means of the blood stream, to the skull, lungs and long bones, whereas those of the right gland, by means of the lymphatics travel to the liver and regional lymph nodes.

It is noted that the vein and lymphatics from the right suprarenal gland run from the upper pole to join the vena cava and main lymphatic trunk, whereas those of the left gland emerge from the lower pole to join with the renal vein and lymphatics.

The symptoms of neuroblastoma are quite varied and depend almost entirely upon the size and position of the primary tumor and their metastatic lesions. Again, since so many cases occur in infants and very young children, exact symptoms and their chronology are frequently difficult to ascertain. In a great many cases it is the parent who, while routinely caring for the child, notices something unusual and so consults a physician. In our case 1 the mother noticed a sudden appearance of right periorbital ecchymosis which prompted her to seek medical aid. In our case 2 the first sign that the child was ill was the fact that he frequently awakened and cried out at night. In our third case the patient developed abdominal pain with

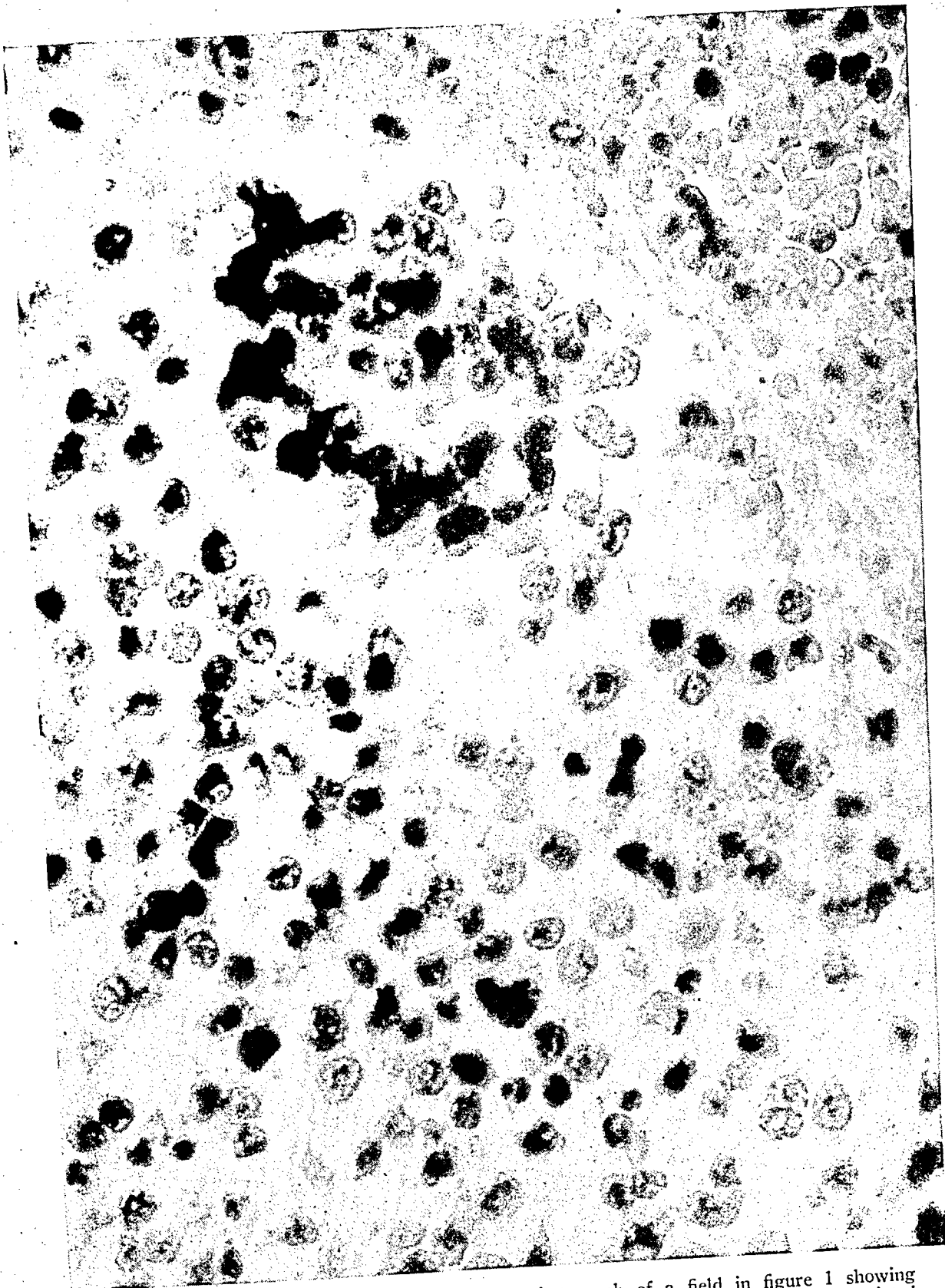


FIG. 3. *Case 1.* High magnification microphotograph of a field in figure 1 showing the atypical rosette and the character of the cells. Note the round, highly undifferentiated cells with hyperchromatic and vesicular nuclei which characterized the cell picture of neuroblastoma found in very young infants. An occasional large, mononuclear cell is seen representing a more mature type of neurocyte. Hematoxylin and eosin stain. $\times 1000$. (U. S. Army Medical Museum Neg. No. 68991.)

nausea and vomiting; a diagnosis of "appendicitis" was made, and an appendectomy was performed.

Shortly after the onset of symptoms most patients develop an abdominal mass on one side or the other which becomes tender and slightly painful. Nausea and vomiting occur frequently. A secondary anemia is quite constant. Fever usually ranges from 99 to 104 degrees F. Pains in affected joints and bones are common, and in many cases exophthalmos with sur-

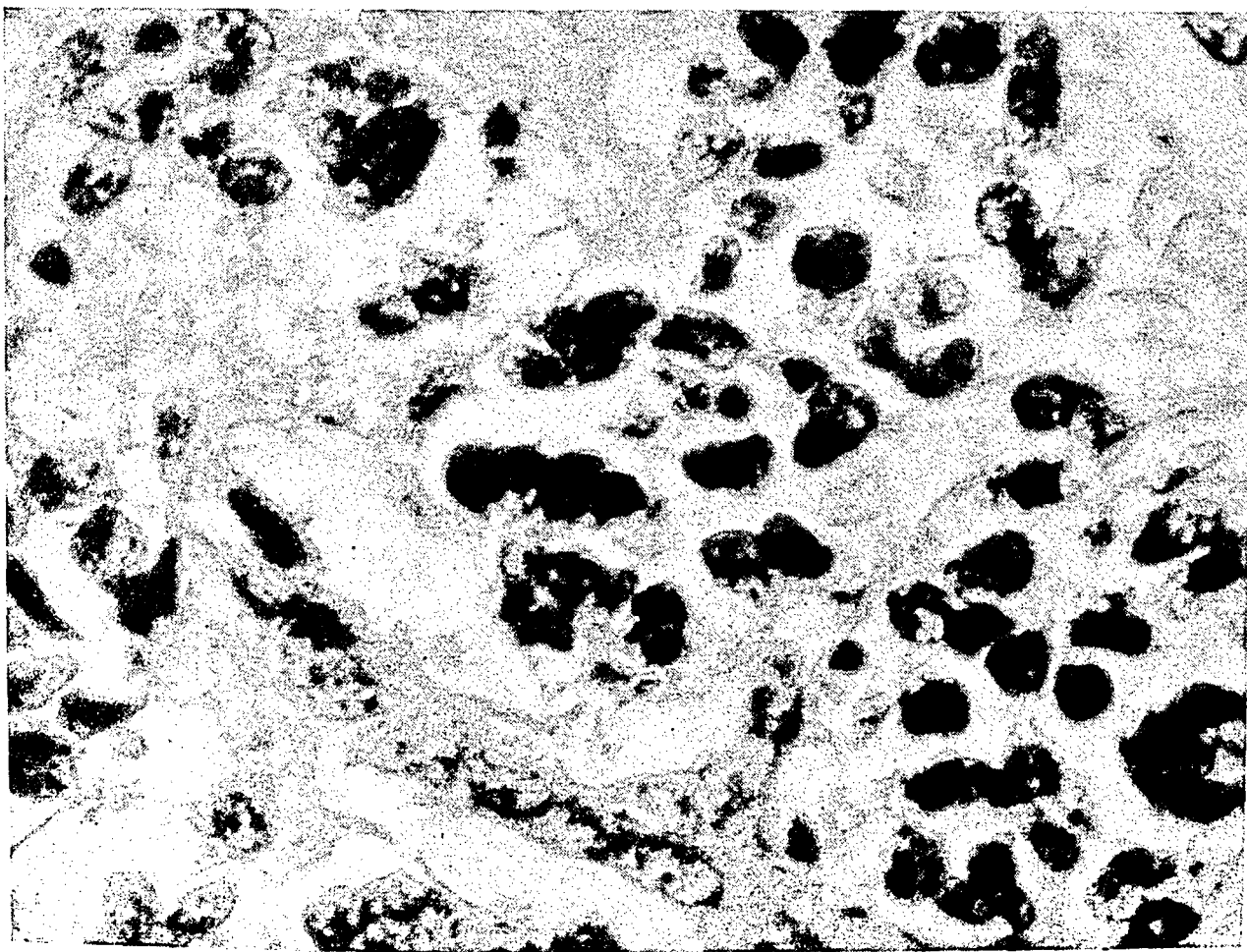


FIG. 4. *Case 2.* High magnification microphotograph of a field in figure 2 showing the spindle and polygonal shaped neuroblasts surrounded by the fibrillar matrix. The nuclei are hyperchromatic and vesicular. An occasional large multinucleated cell is noted. This type cell picture represents a more mature development of the neuroblast and is noted in older children and young adults. Compare with figure 3. Hematoxylin and eosin stain. $\times 1000$. (U. S. Army Medical Museum Neg. No. 68992.)

rounding discoloration of the lids is noted. Diminished activity, pallor, dyspnea, anorexia and emaciation practically always occur, and these become more pronounced as the disease progresses. Lymphadenopathy, in various locations, is usual.

The usual clinical course for this neoplasm is progressively downward, eventually terminating fatally. The number of days' hospitalization in our cases were 40, 191 and 105 days respectively.

The roentgen-ray findings in bone metastases are typical according to Lewis and Geschickter.¹⁰ Scattered, small, multiple areas of rarefaction are usually seen. Of the bones in the body, those of the skull are the most common sites for metastases. The ribs, humerus and femur are commonly affected. In the skull the usual picture is separation of the sutures with scattered small areas of resorption, particularly in the frontal and parietal bones. The metaphysial areas of the long bones are usually the first affected

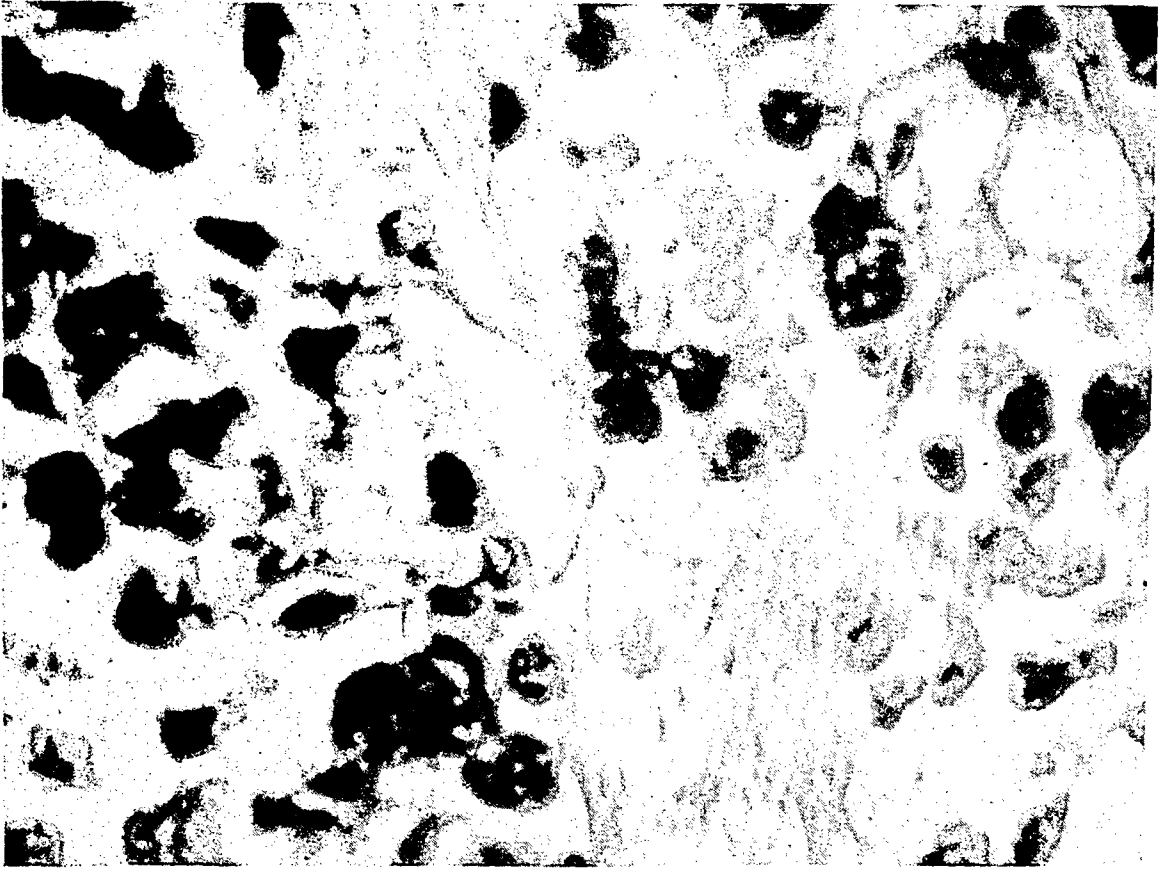


FIG. 5 Case 2. High magnification microphotograph of a field in figure 2 stained with Mallory's phosphotungstic acid hematoxylin method showing the axon-like processes of the cells and the fibrillar matrix. Note the single cell in the upper left quadrant with process pointing to lower right corner. $\times 1000$. (U. S. Army Medical Museum Neg. No. 68993.)

and the areas of resorption are usually wedge-shaped in appearance. There is frequently an overlying periosteal reaction.

The diagnosis of neuroblastoma depends largely upon the metastatic lesions and the presence of an abdominal tumor. In those cases of orbital metastases, with exophthalmos and periorbital ecchymosis, the diagnosis is comparatively easy. The metastatic lesions present a histologic picture identical with that of the primary neoplasm. Contrary to the opinion of many, these tumors are sensitive to irradiation and melt down quite rapidly.

In lymphocytoma, including the leukemic forms, ascites and involvement of the superficial lymph nodes are usual findings. In neuroblastoma ascites almost never occurs.

Kidney tumors, with the exception of the Wilms' tumor, are rare in children and in this latter neoplasm, hematuria and urinary obstruction, along with significant pyelograms, are usually diagnostic. The Wilms' tumor does not metastasize to bones.

Thorough hematologic examinations will usually rule out chloroma, and this disease is rare in children. These studies of the blood, together with lipid studies, examination of the spleen and roentgenograms, aid in the differentiation of Hand-Schüller-Christian disease.

Ewing's tumor seldom occurs before the age of four years and in the bony metastases the characteristic periosteal reaction with the onion peel splitting of the layers is usually present.

Acute surgical abdominal diseases are sometimes confused with neuroblastoma of the suprarenal medulla, but these are usually ruled out with ease after the entire examination of the patient is accomplished. In our third case the symptoms and signs indicated an attack of acute appendicitis for which an appendectomy was performed. Shortly after the appendectomy the abdominal mass became apparent, all signs and symptoms suggested a liver or subdiaphragmatic abscess, and further surgical measures were instituted.

Two of our cases were primary in the right suprarenal gland, and the other occurred in the left. Bilateral involvement has been recorded in several cases in the literature. The size of the tumor is quite variable and is dependent somewhat upon previous irradiation. The neoplasms are usually encapsulated and nodular and they may be solid or cystic. On cut section, the cut surfaces are usually yellowish-red and hemorrhagic, showing scattered areas of necrosis and hemorrhage. The kidney below the tumor mass is usually compressed and only rarely invaded.

The histologic picture of these tumors is quite characteristic. They are very cellular, the cells being of the small round, mononuclear type, containing very little cytoplasm and a large central, hyperchromatic nucleus. These cells occur in small masses or islands separated by strands or trabeculae of fibrils. This fibrillated stroma may be dense in areas and appear as hyaline, fibrous strands. In about 50 per cent of the cases rosette formation (the circular grouping of the cells about a central fibrillated stroma) is noted, but this feature is not as constant as in cases of retinoblastoma of the eye. Pseudo-rosettes (the grouping of cells about small capillaries) have been reported, but this histologic feature was absent in our three cases. Scattered among the small cells are occasional large, round to polygonal spindle shaped cells with vesicular nuclei. These cells have the appearance of the more mature type spongioblast. Occasionally mature ganglion cells or chromaffin cells are present which emphasize their relationship to the small, immature

neuroblasts. Occasionally fibrils, simulating axones, are noted arising from some of the tumor cells and are seen best with the Bielschowsky's neurofibril stain.¹⁵

It is generally concluded that the younger the patient, the less differentiated are the cells in the composition of the tumor, and likewise the greater the malignancy. In the very young the tumor is practically composed of the small round, immature, undifferentiated neuroblasts, while in older children and young adults the cells become polygonal and spindle-shaped, showing a tendency to form the more mature type cells. This feature is noted in comparing our first and second cases.

Multiple tumors of the sympathetic nervous system do occur which illustrate the three types of growth arising from the sympathetic system and represent the three stages in differentiation of the formative neuroblast, namely the neuroblastoma, ganglioneuroma and paraganglioma. Recently, Wahl and Craig,¹⁶ in 1938, reported a case.

As stated previously in this paper, contrary to the opinions of many investigators, irradiation definitely affects these neoplasms. After irradiation the tumors definitely melt down and the life of the patient is prolonged. Although irradiation alters the size and consistency of the tumor, it does not halt metastases. Our second case received a total of 14,500 R and the abdominal mass melted from the size of a child's head down to the point where the tumor, at autopsy, measured 3 by 1.5 by 1.5 cm. The life of this patient was undoubtedly prolonged by the irradiation; however, one of the principal findings at autopsy was the marked aplasia or destruction of the bone marrow. The total leukocyte count just prior to death was 100. Surgery has been attempted in many cases but it is considered to be ineffective. Lehman,⁸ in 1917, reported a case in which a neuroblastoma of the suprarenal medulla was removed in 1916, and the patient was reported well in 1931, 15 years after removal of the neoplasm.

CASE REPORTS

Case 1. A. K., female, aged 17 months, entered W. R. G. Hospital on July 24 and died on September 2, 1939. The chief complaint was abdominal distress and bilateral periorbital ecchymosis. The apparent onset of symptoms was about July 1, 1939, at which time she developed a blue discoloration about the right eye. This was followed shortly by protrusion of the eyeball and a spread of the discoloration to the tissues about the left eye.

The family history was not remarkable except that her maternal grandmother had died of carcinoma of the bladder. Her father, mother and one sister, aged six years, were living and well.

The girl was born at full term with normal delivery; birth weight was seven pounds. Artificial feeding was started after six weeks. She had pertussis in December 1938 and chickenpox in April 1939. No residuals were apparent from either illness.

Upon admission physical examination revealed a poorly nourished white female apparently suffering with abdominal distress. Temperature was 99.4° F. (rectal).

The pulse and respirations were not recorded. The weight was 22 pounds. There was moderate pallor of the skin and mucous membranes, prominent bilateral periorbital ecchymosis with moderate right exophthalmos, and a palpable abdominal mass in the upper left abdominal quadrant.

The patient's illness ran a rapidly progressive unfavorable course. She received symptomatic treatment; and she was given deep roentgen-ray therapy over four areas, total 1180 R, which was discontinued at the request of her mother who felt that the treatment was not beneficial. During the first part of August the patient developed a tumor mass in the right infraorbital region, which spread later to the left antrum, roof of the mouth, gum margins and tongue. During the latter part of August she developed transient soft swellings of the neck and submaxillary regions with progressive bilateral exophthalmos. The patient was unable to take nourishment and at the request of the mother fluids were not given. Inanition became marked and the patient died at 2:55 p.m., September 2, 1939.

Laboratory and Roentgenological Findings: The red cell count varied from 3,500,000 with 65 per cent hemoglobin at the time of admission to 1,240,000 with 50 per cent hemoglobin just before death. The white cell count was not increased; the differential counts varied from 50 to 20 per cent lymphocytes, monocytes 2 to 7 per cent, and polymorphonuclear neutrophils 47 to 80 per cent.

Roentgenograms of ribs, lungs, humeri, femora and proximal half of tibiae and fibulae appeared normal throughout the course. Films of the skull showed suture separation with multiple areas of bone destruction, particularly in the frontoparietal region.

Postmortem Examination. Gross: The body was markedly undernourished and there was marked pallor throughout. Both eyes showed exophthalmos, most marked on the left, with prominent left periorbital ecchymosis. Nodular, soft and necrotic tumor involved the palate, tongue and gum margins, with several upper teeth loose and free in the tumor. There was moderate bilateral cervical adenopathy. No scars or other marks of identification were noted.

A large, soft, hemorrhagic and friable tumor mass was noted almost filling left abdominal cavity. This tumor involved the left suprarenal gland and compressed the left kidney but did not invade it. The mass measured approximately 20 cm. in diameter. Ascites was not present. The tumor was adherent to the omentum, pancreas and parietal peritoneum. The stomach and intestines were normally distended with gas. The liver weighed 345 grams, and the capsule was mottled with grayish-white, irregular, indurated areas of tumor. The organ was firm and upon cut section many scattered, irregular areas of tumor metastasis were noted which appeared yellowish-white in color. The gall-bladder, spleen, right suprarenal, right kidney and remaining genito-urinary organs did not show any significant gross pathologic changes. The mesenteric and abdominal lymph nodes were enlarged and hard, showing gross evidence of tumor metastasis. The gastrointestinal tract, lungs, heart and aorta were not remarkable. Permission was not granted to examine thoroughly the head and neck.

Microscopic Study: Various sections from the tumor mass involving the left suprarenal gland and the metastatic lesions in the liver and lymph nodes showed similar pictures. Large and small irregular masses and clumps of small, round to polygonal cells with little cytoplasm and large hyperchromatic and vesicular nuclei were present which were separated by imperfect strands and trabeculae composed of parallel fibrils. Areas of hemorrhage and necrosis were present. An occasional imperfect rosette formation was noted, and scattered among the small round cells were occasional large round and spindle cells with vesicular nuclei.

In addition to the metastatic sites already mentioned, various sections of the lungs showed the presence of very small foci of tumor cells similar to those found in the main neoplastic mass.

Case 2. R. A. W., male, aged five years, entered W. R. G. Hospital on March 17 and died September 26, 1938. The chief complaints upon admission were loss of weight, weakness, nausea, vomiting, bone pains, and a tumor mass in the right abdomen. The apparent onset of symptoms occurred about September 10, 1937 with cramping epigastric pains. For several weeks prior to this the mother observed that the child would frequently cry out while asleep. During the latter part of September 1937 the patient developed pain in the extremities, particularly in the right arm and left thigh. A progressive pallor developed, and in January 1938 a tumor mass was felt in the abdomen to the right of the umbilicus, without ascites, together with a bilateral cervical and postauricular lymphadenopathy and a nodular swelling over the right frontal region. According to the mother the patient ran a fever ranging from 99 to 102° F. for from 7 to 10 days alternating with afebrile periods of from 3 to 12 days.

The family history and past history were not pertinent.

Upon admission physical examination revealed an emaciated white male about the stated age, appearing in extremis. Temperature was 104° F., pulse 104, and respirations 24. Length was 44 inches and weight 34 pounds. The skin was pale yellow and waxy. The lymph glands of the neck, axillae and groin were enlarged and hard. A tumor mass about 10 cm. in diameter was palpated in the right abdomen. There was wasting of the muscles of both thighs. Blood pressure was 94 mm. Hg systolic and 78 mm. diastolic. The lungs and heart were not remarkable.

The progress of the patient in the hospital was progressively downward. He received symptomatic treatment with deep irradiation over several areas, totalling 14,500 R up until date of death. Following irradiation the tumor masses decreased in size markedly. The patient failed progressively and died on September 26, 1938 at 6:30 a.m.

Laboratory and roentgenological findings: The red cell count varied from 2,800,000 with 55 per cent hemoglobin upon admission to 1,500,000 with 25 per cent hemoglobin before death. The total leukocyte count dropped as low as 100 with definite lymphocytic preponderance. Urine examinations were not remarkable.

Numerous roentgenograms showed scattered areas of rarefaction in all the long bones and in the skull. Following irradiation some recalcification occurred in many areas.

A biopsy of a cervical lymph gland on March 19, 1938 confirmed the clinical diagnosis of neuroblastoma.

Postmortem Examination. Gross: The body was markedly emaciated and showed prominent pallor. There was moderate exophthalmos of the right eye with surrounding soft tissue ecchymosis. There was definite generalized lymphadenopathy.

The right suprarenal gland was involved in a tumor mass measuring 3 by 1.5 by 1.4 cm., after much irradiation. This tumor was soft, friable and hemorrhagic. The left suprarenal and kidneys were not involved. The mesenteric and abdominal lymph nodes were large and showed gross tumor metastasis. The liver was large, weighing 675 grams. Numerous pale yellowish-red metastatic foci were present on the capsular surface as well as in the parenchyma. The gall-bladder and spleen were not remarkable. Both testes were large, nodular and on cut section showed the organs to be replaced by tumor. Metastatic foci, nodular in character, were noted on the pleural surfaces, and in the lung parenchyma were many scattered, ill defined areas of hemorrhagic infiltration varying from 1 to 4 cm. in diameter. In the centers of these areas a paler, pink translucent tissue was seen. About 125 c.c. of thin, sanguinous fluid were noted in the pericardial sac and scattered small hemorrhagic foci were noted on the epicardium. These foci did not involve the myocardium. The heart weighed 135 grams. The aorta was not remarkable.

The distal end of the right femur, beginning approximately 15 cm. above the articular surface, showed a gradual enlargement of the bone with aplasia of the bone marrow. Permission was not granted for examination of the skull and contents.

Microscopic Study: The tumor was composed of masses of hyperchromatic polygonal cells, sometimes assuming a spindle shape, having large, densely stained nuclei and scanty cytoplasm. These masses were surrounded by rather dense fibrillated stroma. Occasionally they appeared to form incomplete acini but nothing that could be designated a rosette was seen. All metastatic lesions showed a similar histologic picture.

Case 3. H. A. M., male, aged 18 years, was admitted to the hospital on July 17 and died on November 10, 1936. The chief complaints upon admission were pain and tenderness in the lower right quadrant, nausea and vomiting. Temperature was recorded at 99.2° F., and the total leukocyte count was 12,500 with 69 per cent polymorphonuclear leukocytes. A diagnosis of appendicitis was made, and the appendix was removed but showed no remarkable pathologic changes. The patient's condition did not improve after operation and on September 8, 1936 a large, moderately firm and tender tumor mass was noticed filling the entire upper right abdominal quadrant to the midline and down to the umbilicus. The history and physical examination indicated a subphrenic or liver abscess and on September 14, 1936 the abdomen was again opened, at which time a large tumor mass was noted which was retroperitoneal and involved the right lobe of the liver.

The family and past history were not pertinent.

The course of the patient in the hospital was progressively downward. Emaciation developed steadily as did a secondary anemia. The operative wound drained freely and frequent dressings per day were applied. Fever from 99° to 102° F. persisted. Examination of the heart and lungs showed no pathologic changes. The tumor mass in the abdomen became progressively larger. The treatment was purely symptomatic. The patient became weaker each day and died on November 10, 1936 at 3:30 a.m.

Laboratory and roentgenological findings: Urine and feces examinations were repeatedly within normal limits. Blood counts constantly showed an average leukocyte count of about 12,000 with 69 per cent polymorphonuclear leukocytes. There was also a progressive "shift to the left." The red cell count dropped to 1,300,000 with 38 per cent hemoglobin. Various blood chemistry examinations and repeated Wassermann and Kahn reactions were all negative.

Numerous roentgenograms of the bones of the body were all negative. Plates on October 17, 1936 showed the right leaf of the diaphragm to be extremely high, the right lung compressed, and marked pleural thickening along the lower half of the chest in the axillary line. No deep irradiation was given.

Postmortem Examination: The body was markedly emaciated, with a length of 62 inches and estimated weight of 55 pounds. The upper right half of the abdomen was distended and the right side of chest became bulged owing to prominent flaring of the ribs. A longitudinal, recent surgical incision about six inches in length was present in the right hypochondrium.

In the right retroperitoneal space a large, soft, friable and hemorrhagic tumor mass about the size of a man's head was noted which was adherent to and continuous with the right lobe of the liver. This mass compressed the right kidney and pushed all abdominal structures to the left. Traces of suprarenal gland were noted at the upper pole of the right kidney, the greater portion of the gland being replaced by tumor. Ascites was not present. Small nodules of tumor metastasis were noted on the parietal peritoneum and two small nodules were noted in the lower lobe of the left lung.

All other viscera, together with all bones, were essentially normal.

Microscopic Study: Sections of tumor showed masses and islands of small and irregular cells with very little cytoplasm and with large, 'hyperchromatic nuclei. These masses were partially set off and trabeculated by longitudinal groups of thin fibrils. An occasional rosette was noted. The tumor was quite vascular and scattered areas of hemorrhage were present along with scattered areas of necrosis.

CONCLUSIONS

1. Neuroblastoma of the suprarenal medulla is a definite pathologic entity and is relatively rare. About 220 cases have been reported in the literature; three additional cases of our own are added.

2. Too much emphasis has been placed upon the so-called clinical syndromes of Pepper and Hutchinson. The histologic picture of each type is identical, and from a survey of the cases reported there is much overlapping of the criteria. In about 20 per cent of the cases a definite classification is impossible.

3. Sex is not a factor in the incidence of these tumors and in general, the younger the patient, the more undifferentiated are the tumor cells and the greater is the degree of malignancy.

4. The symptoms depend entirely on the position, size and extent of the primary tumor, together with the location of the metastases. The usual clinical course is progressive with rapidly fatal termination.

5. The tumor is sensitive to irradiation, contrary to general opinion, and this treatment prolongs the course of the case. Although one case is reported in the literature as well 15 years after surgical removal of the suprarenal tumor, it is generally concluded that surgery is not of benefit.

BIBLIOGRAPHY

1. VIRCHOW, R.: *Die krankhaften Geschwülste*, A. Hirschwald, Berlin, 1864, ii, p. 150.
2. MARCHAND, F.: *in Internationale Beiträge zur wissenschaftlichen Medizin: Festschrift, R. Virchow gewidmet zur Vollendung seines 70 Lebensjahres*, Berlin, 1891, i, p. 578.
MARCHAND, F.: Über eine eigenthümliche Erkrankung des Sympathikus, der Nebennieren end der peripherischen Nerven (ohne Bronzehaut), *Virchow's Arch. f. path. Anat.*, 1880-1881, 477-502.
3. KUSTER, H.: Über Gliome der Nebennieren, *Virchow's Arch. f. path. Anat.*, 1905, clxxx, 117.
4. WRIGHT, J. H.: Neurocytoma or neuroblastoma, a kind of tumor not generally recognized, *Jr. Exper. Med.*, 1910, xii, 556-561.
5. FREW, R. S.: On carcinoma originating in the suprarenal medulla in children, *Quart. Jr. Med.*, 1910-1911, iv, 123.
6. WAHL, H. R.: Neuroblastoma with a study of a case illustrating the three types, *Jr. Med. Research*, 1914, xxx, 205.
7. DUNN, J. S.: Neuroblastoma and ganglioneuroma of the suprarenal body, *Jr. Path. and Bact.*, 1915, xix, 456.
8. LEHMAN, E. P.: Neuroblastoma with report of a case, *Jr. Med. Research*, 1917, xxxvi, 309.
9. SCOTT, E., OLIVER, M. G., and OLIVER, M. H.: Sympathetic tumors of the adrenal medulla, *Am. Jr. Cancer*, 1933, xvii, 396-433.

10. LEWIS, DEAN, and GESCHICKTER, C. F.: Tumors of the sympathetic nervous system, *Arch. Surg.*, 1934, xxviii, 16-58.
11. REDMAN, J. L., AGERTY, H. A., BARTHMAIER, O. F., and FISHER, H. R.: Adrenal neuroblastoma, *Am. Jr. Dis. Child.*, 1938, lvi, 1097-1112.
12. WEICHSELBAUM, H.: Über Gliome der Nebennieren, *Virchow's Arch. f. path. Anat.*, 1905, clxxx, 117.
13. PEPPER, W. A.: A study of congenital sarcoma of the liver and suprarenal, *Am. Jr. Med. Sci.*, 1901, cxxi, 287.
14. HUTCHINSON, R.: Suprarenal sarcoma in children with metastases to skull, *Quart. Jr. Med.*, 1907, i, 33.
15. MALLORY, F. B.: *Pathologic technique*, 1938, W. B. Saunders Co., Philadelphia, 222-223.
16. WAHL, H. R., and CRAIG, P. E.: Multiple tumors of the sympathetic nervous system, *Am. Jr. Path.*, 1938, xiv, 797-808.

CASE REPORTS

HEMOPHILUS INFLUENZAE BACTEREMIA: REPORT OF TWO CASES RECOVERING FOLLOWING SULFATHIAZOLE AND SULFAPYRIDINE*

By CHESTER S. KEEFER, M.D., F.A.C.P., and CHARLES H. RAMMELKAMP, M.D.,
Boston, Massachusetts

RECENTLY we have observed two patients with *Hemophilus influenzae* bacteremia who recovered following chemotherapy. One patient had pneumonia and the other had a primary lesion in the biliary passages. Since *H. influenzae* infection of the bile passages was unique in our experience, we were stimulated to review the subject of *H. influenzae* bacteremia in general as well as to report our recent experience.

CASE REPORTS

Case 1. A young man with lobar pneumonia, H. influenzae in the sputum and circulating blood, recovers promptly following sulfapyridine.

A white man, 30 years of age, was admitted to hospital complaining of fever, cough, and pain in the chest which was exaggerated by respiratory effort. Aside from the fact that he had had a head cold and a slight cough for two weeks before his acute illness, he had been well. Twenty-four hours before admission he had a chill which was followed by high fever, increasing cough, bloody sputum, and pain in the right chest.

On examination, the temperature was 103° F., the pulse rate 120 per minute, and the respirations 30 per minute. Moderate cyanosis was present and there were signs of pneumonia over the right middle and upper lobes.

The laboratory examinations showed a leukocytosis of 23,400 per cubic millimeter. There were many *H. influenzae* in the sputum but no pneumococci. The roentgen-ray examination of the chest confirmed the diagnosis of pneumonia and the blood culture was positive for *H. influenzae*.

The course of the illness is shown in figure 1. Following the use of sulfapyridine, the blood was cleared of organisms and the temperature gradually declined to normal. There were no complications.

This case, then, is an example of *H. influenzae* pneumonia following an upper respiratory infection in which there was consolidation of two lobes of the right lung and bacteremia. Recovery without complications followed treatment with sulfapyridine.

H. influenzae infections of the lungs are more often secondary to some other infection, such as influenza virus infection, or they occur as mixed infections of the lung. They may be isolated from the sputum of patients with lung abscess, bronchiectasis, or other chronic infections of the lung, and occasionally they are secondary invaders in tumors of the lung. Occasionally they cause pneumonia

* Received for publication April 16, 1941.

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

without preceding infection. These infections played a prominent part in some of the cases of pneumonia following the pandemic of influenza in 1918 and, indeed, by some students of the pandemic they were considered to be responsible for the epidemic itself. That these organisms may cause serious infections there is no doubt. Whether the experience in this isolated case of pneumonia will be confirmed in others with the same infection and bacteremia following sulfapyridine, only time will tell.

B. INFLUENZAE PNEUMONIA

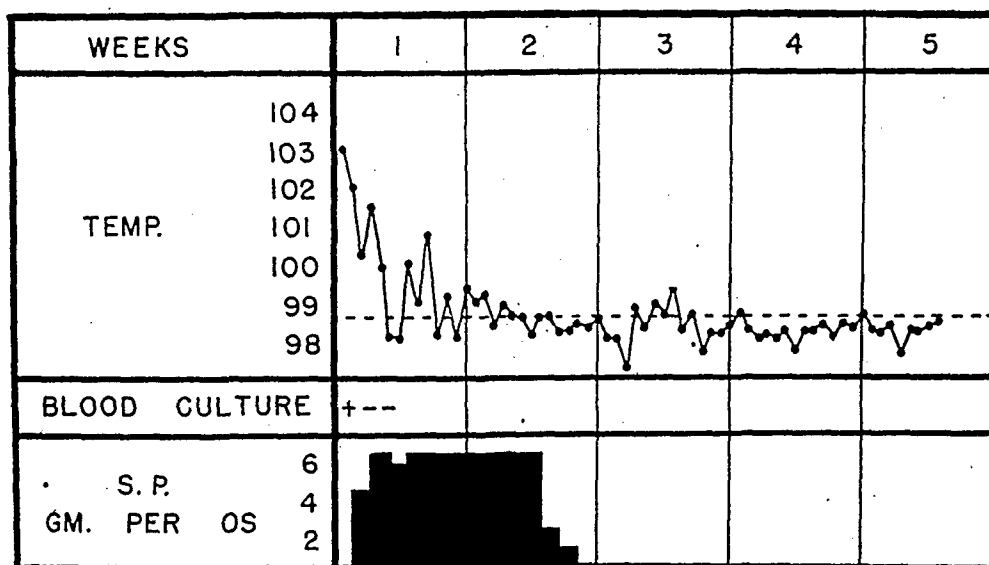


FIG. 1.

S. P. = Sulfapyridine.

Case 2. A young man has repeated attacks of biliary colic with jaundice; then chills, fever, jaundice, hepatomegaly, splenomegaly, H. influenzae bacteremia. The blood was temporarily sterilized by sulfathiazole. Complete recovery followed cholecystectomy and drainage of common bile duct.

A 34 year old, white chef entered the Evans Memorial March 21, 1940, complaining of recurrent jaundice associated with mid-epigastric pain, chills, fever and vomiting. His present illness began about two years before at which time he began to have frequent nocturnal attacks of indigestion, which were characterized by sharp, colicky, mid-epigastric pain, which did not radiate. The following day, the urine would be dark brown in color. One year previous to entry he had a sudden onset of jaundice associated with mid-epigastric and right-sided pain of three weeks' duration. He finally recovered from this attack. His immediate present illness began nine days before we saw him, and it was characterized by gradually deepening jaundice, intermittent chills and fever, dark urine, and light-colored stools. He had had an attack of pneumonia with pleurisy at the age of seventeen. He had always been overweight and at the age of 26 he weighed 238 pounds. Two weeks before entry to this hospital he weighed 195 pounds.

On admission, the general physical examination revealed a well-developed and well-nourished man who was deeply jaundiced, but in no apparent distress. The temperature was 99°. The skin and mucous membranes were yellow. There were several telangiectatic spots over the nose and back of the hands. The skin was warm and dry, and there were many excoriations over the upper arms, abdomen and thighs,

which resulted from excessive scratching. The heart and lungs were clear. Blood pressure was 126 mm. Hg systolic and 72 mm. diastolic. The abdomen was well developed and symmetrical. There was definite tenderness just to the right of the mid-epigastrium. The spleen was easily palpable four fingers' breadth below the costal margin. The liver was felt about six centimeters below the costal margin, was smooth in outline and moderately tender. Gall-bladder was not felt. Genitalia were normal. Rectal examination was negative. There was a scar of an old varicose vein with considerable pigmentation over the inner aspect of the lower half of the left leg; otherwise, the extremities were normal.

The essential laboratory data were as follows: The urine showed albumin, bilirubin, and urobilinogen. With the exception of a leukocytosis of 18,700 the blood

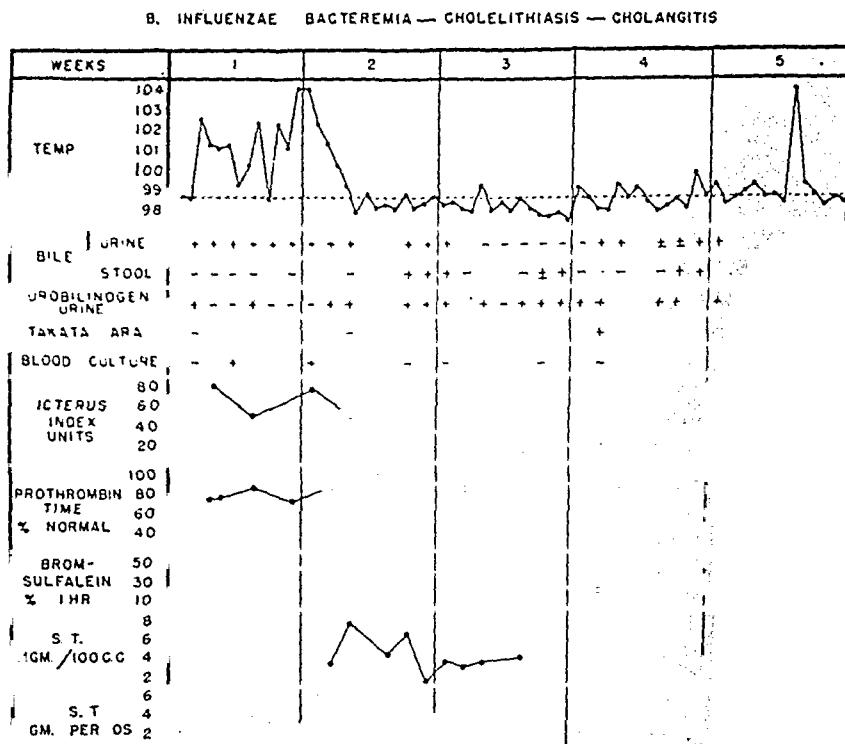


FIG. 2.

S. T. = Sulfathiazole.

was normal. The icterus index was increased to 80 pigment irregularly. The other laboratory examination

By roentgen-ray examination a flat film of the abdomen showed a calculus in the gall-bladder. The intravenous Graham method of the dye in the gall-bladder, but there was no definite

The course of the patient's illness is shown in figure 2. There was high, irregular fever. The urine contained bile and the icterus index was elevated. The prothrombin time and the bromsulphalein test showed a decreased excretion of the dye that he had an *H. influenzae* bacteremia, sulfathiazole was given averaging four grams a day. Following this treatment the temperature was normal, and the patient showed temporary improvement. There was no fever and jaundice so that an operation was advised. Dr. How

and found a cholecystitis and cholelithiasis with stones in the common duct and cholangitis. Following operation he made a satisfactory recovery and has remained well.

In the present case, the outstanding features were the recurrent attacks of biliary colic with jaundice; chills and fever with leukocytosis; enlargement of the liver and spleen; bacteremia due to *Hemophilus influenzae* which could not be typed; sterilization of the blood following the exhibition of sulfathiazole; complete recovery following cholecystectomy with drainage of the common bile duct and removal of stones.

In our experience, the isolation of *H. influenzae* from the circulating blood in patients with cholangitis and cholelithiasis was unique. Upon looking into the matter, however, we found that Ophüls¹ had described multiple liver abscesses which were owing to organisms like the influenza bacillus and which were secondary to an infection of the rectum, but we have been unable to find cases of cholangitis secondary to stones resulting from influenza bacillus infection. In view of the fact that these organisms occur so seldom in infections of the liver, the features of *H. influenzae* infection and bacteremia in general are reviewed.

REVIEW OF *H. Influenzae* INFECTION

The *Hemophilus influenzae* bacillus is frequently found in the throat of normal individuals. Once it leaves this habitat it may invade the meninges, the lungs, the circulating blood, the joints, the endocardium, or the kidneys. Indeed, localized infections of various organs of the body, including the throat, liver, or genital organs, have been described. Since several of these infections are of importance they require special comment.

Meningitis. Meningitis caused by the *Hemophilus influenzae* is accompanied by bacteremia in 70 per cent of cases when the blood is cultured early in the course of the disease. Most of the cases occur in children under the age of three years and the fatality rate following serum and chemotherapy has been greatly reduced.² The organisms causing this infection almost always are Type B bacilli. If the patient lives long enough to develop metastases they are usually in the joints, and the involvement is generally polyarticular rather than monarticular.

Arthritis. Many of the cases of *H. influenzae* arthritis have been reviewed by Weaver and Sherwood³ who divided the cases into two groups: (1) those associated with meningitis and (2) those with arthritis alone. They stress the fact that most of the patients are under two years of age although one of their patients was 59 years of age, and other cases have been reported in adults. In the cases of arthritis following meningitis the outcome was usually fatal and the arthritis was a polyarthritis. In the cases without meningitis, recovery was the rule and the arthritis was more likely to be monarticular. In a few cases of arthritis caused by this organism, the original process was in the bone and the infection spread to involve the joints as a secondary process.

Endocarditis. It has long since been recognized that the influenza bacillus is one of the infecting organisms in subacute bacterial endocarditis.^{4, 5, 6} There is nothing peculiar or characteristic about the bacterial endocarditis caused by this organism since renal complications, mycotic aneurysms, and the other fea-

tures of infective endocarditis may also be observed in influenza bacillus infections.^{4,5,6}

Kidney Lesions. Aside from the cases of focal embolic glomerular nephritis owing to the influenza bacillus, Albright, Dienes and Sulkowitch⁷ have described cases of pyelonephritis with nephro-calcinosis caused by *Hemophilus influenzae* which were relieved by sulfanilamide. The calcium deposits in the kidney were disclosed by roentgen-ray examination and they were unequal in size and much larger than the calcium deposits which are seen in hyperparathyroidism. The urine in these cases is alkaline and, as long as the infection persists, it remains so. Other reports of infections of the kidney by this group of organisms have been made by Burkland and Leadbetter,⁸ Davis,⁹ and Wright.¹⁰

Throat Infections. Influenzae bacillus bacteremia following infections of the throat have been described by Frank,¹¹ Koch,¹² Lemierre, Meyer and Laplane,¹³ and Hotz.¹⁴ In the case described by Frank, a 19-year-old boy developed *H. influenzae* bacteremia following a bilateral tonsillitis with retrotonsillar abscess, thrombosis of the maxillary and internal jugular vein, and metastatic abscesses in the lungs and pleura. This was a typical case of posttonsillitis thrombophlebitis which made its appearance seven days after the primary illness had apparently subsided.

In the first case described by Lemierre, Meyer and Laplane¹³ there was an ulcerative pharyngitis, bronchopneumonia, bullous lesions of the neck, and arthritis of the sternoclavicular joint. Influenza bacilli were isolated from the blood, the throat, and the bullous lesion of the skin. He considered this case to be one of posttonsillitis sepsis. It is plain, then, that the influenza bacillus is one of the organisms which can cause thrombophlebitis of the deep cervical veins and bacteremia with multiple abscesses.

Of considerable interest are the cases of influenza bacillus pericarditis which begin as a sore throat and signs of laryngeal stenosis. Hotz¹⁴ described such a case and collected others from the literature. In brief, the illness begins with a catarrhal sore throat which is soon followed by acute inflammation of the larynx with symptoms and signs of stenosis. These signs may disappear with only slight improvement in the general condition of the patient. Then signs of pulmonary, pericardial, or mediastinal infection follow. It is quite possible that the influenza bacillus is a secondary invader in these cases, since acute inflammatory lesions of the larynx with stenosis are not infrequent in children without influenzal infection.

Puerperal Sepsis. Occasional cases of puerperal sepsis have been reported as a result of infection with the influenza bacillus^{15,16} and local infections of Bartholin's glands¹⁷ or of the Fallopian tubes have been reported. Nye¹⁸ has isolated *Hemophilus influenzae*-like bacilli from the normal cervix and vagina and from the circulating blood of patients with puerperal sepsis so that there seems to be no doubt that these organisms, which can also be found in the stools of some patients, may cause puerperal sepsis in some cases.

Infection of the Conjunctivae. Leichtentritt and Schober¹⁹ described a case of *H. influenzae* bacteremia associated with a relapsing skin eruption, parotitis, and arthritis. The patient was a four year old child who developed a bilateral conjunctivitis which was followed within eight days by high irregular fever and a skin eruption over the face and extremities, maculo-papular urticaria in type.

H. influenzae were isolated from the circulating blood on three occasions. The patient recovered after an illness of six weeks' duration.

Influenza Bacillus-Like Organisms from the Appendix. Hudacsek and Kerbler²⁰ have recorded the isolation of influenza bacilli from the appendices of patients with appendicitis and from peri-appendiceal abscesses. This paper stresses the fact that these organisms occur in the gastrointestinal tract and it is possible that invasion of the biliary tract, the liver, or the genitourinary tract may occur from this source.

COMMENT

From this discussion of *Hemophilus influenzae* bacteremia, it would seem clear that these organisms may enter the circulating blood from the nasopharynx, the lungs, the meninges, or the bile passages. They may be found in the nose and throat, the gastrointestinal tract, and in the vagina of normal individuals. Once bacteremia is established, metastatic foci of infection may be set up in the joints, endocardium, or kidney.

Local infections have been described in the meninges, endocardium, throat, lungs, pericardium, kidney, liver, the rectum and genital tract in men and women.

Bacteremia associated with meningitis is frequently a fatal disease. There is recent evidence, however, to suggest that intensive treatment with rabbit serum and sulfanilamide will reduce the fatality rate in this disease especially in children over three years of age.²

Bacteremia associated with arthritis without meningitis has a good prognosis, largely because the infection tends to focalize in the joints where drainage of the focus of infection can be done effectively.³

The renal infections due to this organism respond favorably to sulfanilamide.

In any case of *H. influenzae* bacteremia, then, sulfathiazole should be used at once. If meningitis is present, it is perhaps well to use sulfanilamide or sulfapyridine since these drugs are found in the meninges in much higher concentration than sulfathiazole. In addition to chemotherapy, intensive intravenous serum treatment should be used.

We have reported two cases of *H. influenzae* bacteremia which recovered following chemotherapy. In one the original focus of infection was the lungs and, in the other, it was the biliary tract.

A brief review of *H. influenzae* bacteremia is presented.

Since this paper was written, Sinclair's report²¹ of *H. influenzae* type B in acute laryngitis with bacteremia has appeared. The organisms were isolated from the blood in all cases and four out of ten patients died. Half of the children were over five years of age. The disease was characterized by an acute onset with fever, leukocytosis, the history of a severe sore throat, the evidence of laryngitis, and the signs of "shock" due to the infection and the laryngeal obstruction. Tracheotomy, sulfonamide and specific serum therapy are all important therapeutic measures.

REFERENCES

1. OPHÜLS, W.: A statistical survey of 3000 autopsies, 1936, Stanford University Publications, Vol. 1, No. 3, p. 204.
2. ALEXANDER, H.: Treatment of bacterial meningitis, Bull. New York Acad. Med., 1941, xvii, 100.

3. WEAVER, J. B., and SHERWOOD, L.: Hematogenous pyarthrosis due to *Bacillus haemophilus influenzae* and *Corynebacterium xerosis*, Surgery, 1938, iv, 908.
4. MILLER, C. P., and BRANCH, A.: Subacute bacterial endocarditis due to hemolytic hemophilic bacillus, Arch. Int. Med., 1923, xxxii, 911.
5. THAYER, W. S.: Bacterial or infective endocarditis, Edinburgh Med. Jr., 1931, xxxviii, 237, 307; Studies on bacterial infective endocarditis, Johns Hopkins Hosp. Rep., 1926, xxii, 1.
6. LIBMAN, E.: A study of endocardial lesions of subacute bacterial endocarditis with particular reference to healing or healed lesions with clinical notes, Am. Jr. Med. Sci., 1912, cxliv, 313; The clinical features of cases of subacute bacterial endocarditis that have spontaneously become bacteria-free, Am. Jr. Med. Sci., 1913, cxlvi, 625.
7. ALBRIGHT, F., DIENES, L., and SULKOWITCH, H. W.: Pyelonephritis with nephrocalcinosis caused by *Haemophilus influenzae* and alleviated by sulfanilamide: report of two cases, Jr. Am. Med. Assoc., 1938, cx, 357.
8. BURKLAND, C. E., and LEADBETTER, W. F.: Pyelitis cystica associated with an *Haemophilus influenzae* infection in the urine, Jr. Urol., 1939, xlii, 14.
9. DAVIS, J. D.: A hemophilic bacillus found in urinary infections, Jr. Infect. Dis., 1910, vii, 599.
10. WRIGHT, J. D.: An observation on the occurrence of the bacillus of influenza (*Bacterium influenzae*) in pyelonephritis, Boston Med. and Surg. Jr., 1905, clii, 496.
11. FRANK, H.: Thrombophlebitische Sepsis nach Angina mit influenza Bazillen im Blut, München. med. Wchnschr., 1933, lxxx, 214.
12. KOCH, F.: Influenzabakterien-Sepsis, München. med. Wchnschr., 1932, lxxix, 706.
13. LEMIERRE, A., MEYER, A., and LAPLANE, R.: Les septicémies a bacille de Pfeiffer, Ann. de méd., 1936, xxxix, 97.
14. HOTZ, A.: Influenzabazillen-Perikarditis, eingeleitet durch Kehlkopfstenose, Schweiz. med. Wchnschr., 1939, xx, 1023.
15. THALER, H.: Ueber eine genitale Infektion mit Influenzabazillen als Ursache eines Fiebers nach der Geburt, Wien. klin. Wchnschr., 1917, xxx, 512.
16. THALER, H., and ZUCKERMANN, H.: Ueber eine genitale Influenzainfektion bei einer Gebärenden als Ursache eines Puerperalfiebers, Monatschr. f. Geburtsh. u. Gynaek., 1915, xli, 377.
17. KOCH, F. E., and KRAMER, E.: Influenzabakterien bei Bartholinitis, München. med. Wchnschr., 1931, lxxviii, 1131.
18. NYE, R. N.: Unpublished observations.
19. LEICHTENTRITT, B., and SCHÖBER, W.: Influenzabacillensepsis mit rezidivierendem Exanthem, Klin. Wchnschr., 1924, iii, 1029.
20. HUDACEK, E., and KERBLER, F.: Beiträge zur Kenntnis der Bakteriumflora des Wurmfortsatzes, mit besonderer Berücksichtigung des Pfeifferschen Influenzabacillus, Arch. f. klin. Chir., 1930, cxi, 540.
21. SINCLAIR, S. E.: *Haemophilus influenzae* type B in acute laryngitis with bacteremia, Jr. Am. Med. Assoc., 1941, cxvii, 170.

BRUCELLA ENDOCARDITIS OF CONGENITAL BICUSPID AORTIC VALVE*

By HARRY F. WECHSLER, M.D., and EINAR G. GUSTAFSON, M.D.,
New York, N. Y.

A review of cases of brucellosis with endocarditis recently was reported by Smith and Curtis.¹ This entity, despite the prevalence of undulant fever in this country, seems still to be a rarity. Of the 10 cases reported, only five^{1,3} have occurred in the United States. The present case is reported because of its rarity and also because it is the first recorded to have been superimposed on a congenital valvular lesion. In addition the pathological changes in the other viscera are of interest.

CASE REPORT

C. W., aged 28, white male, was admitted to the Lenox Hill Hospital on February 24, 1940. He was born in Germany but left there at the age of 10 for South America where he stayed seven years. In 1929 he came to the United States and worked on a farm until his present admission. In 1928 he had chest pain, dyspnea and a productive cough for one month and was said to have had a "heart attack." Since 1928 he had had slight dyspnea on moderate exertion but no other symptoms of loss of cardiac reserve.

His present illness began in December 1939 when he developed a sore throat, dizziness, weakness and frequency of urination. He was seen by a physician and told he had kidney trouble. He improved in three weeks' time. In late January 1940 he developed another sore throat, associated with chills, fever and anasarca. Oliguria and frequency of urination were present. In one week's time the edema subsided but the chills and fever persisted. His dyspnea, however, became more pronounced.

On admission to the Lenox Hill Hospital his temperature was 104° F., respirations 28, pulse 90. He appeared acutely and chronically ill, was moderately dyspneic and orthopneic. There was no evidence of jaundice, cyanosis or petechiae.

The eyes showed slight puffiness of the lower lids. The tonsils were prominent and cryptic, the pharynx was granular and injected, the uvula was bifid. Examination of the neck showed marked arterial pulsation. The lungs showed no abnormal findings.

The heart was enlarged to the anterior axillary line in the fifth intercostal space. Systolic thrills were palpable at both base and apex. A precordial heave was present. At the apex there was audible a harsh systolic blow which was transmitted to the axilla and was followed by a short, soft blowing diastolic murmur. At the base also loud systolic and diastolic murmurs were heard. An inconstant to and fro pericardial friction rub was present. The rhythm was regular. The blood pressure was 105 mm. Hg systolic and 80 mm. diastolic.

The abdomen was soft and relaxed. The liver was enlarged to three fingers' breadth below the costal margin and the spleen to two fingers' breadth. The latter was moderately tender. Slight clubbing of the finger nail beds was present, and a one plus pitting edema of the pretibial region was found. The genitalia were normal.

Admission Laboratory Data: Hemoglobin 66 per cent, red blood cells 4.05 million, white blood cells 9,300 with 58 per cent neutrophils, 40 per cent lymphocytes and 2 per cent monocytes. Urine: Specific gravity 1.020; albumin 4 plus; glucose negative;

* Received for publication November 12, 1940.

From the Medical Service of Dr. Otto M. Schwerdtfeger, Lenox Hill Hospital.

acetone one plus. Microscopically 10 to 15 red blood cells, 5 to 8 white blood cells and numerous hyalin casts per high power field were found.

Blood Chemistry: Urea 41.6 mg. per cent; creatinine 3.2 mg. per cent; uric acid 4.8 mg. per cent; glucose 81 mg. per cent; CO₂ combining power 35.7 volumes per cent.

The stool examination was negative for blood.

Erythrocyte sedimentation rate was 22 mm. in 15 minutes (normal 5 mm.).

Blood Wassermann test was negative.

Course: The patient was in an extremely toxic condition. Repeated blood cultures taken on routine agar media showed no growth. Ten days after admission an agglutination for *B. melitensis* was reported positive in dilutions as high as 1 to 500.

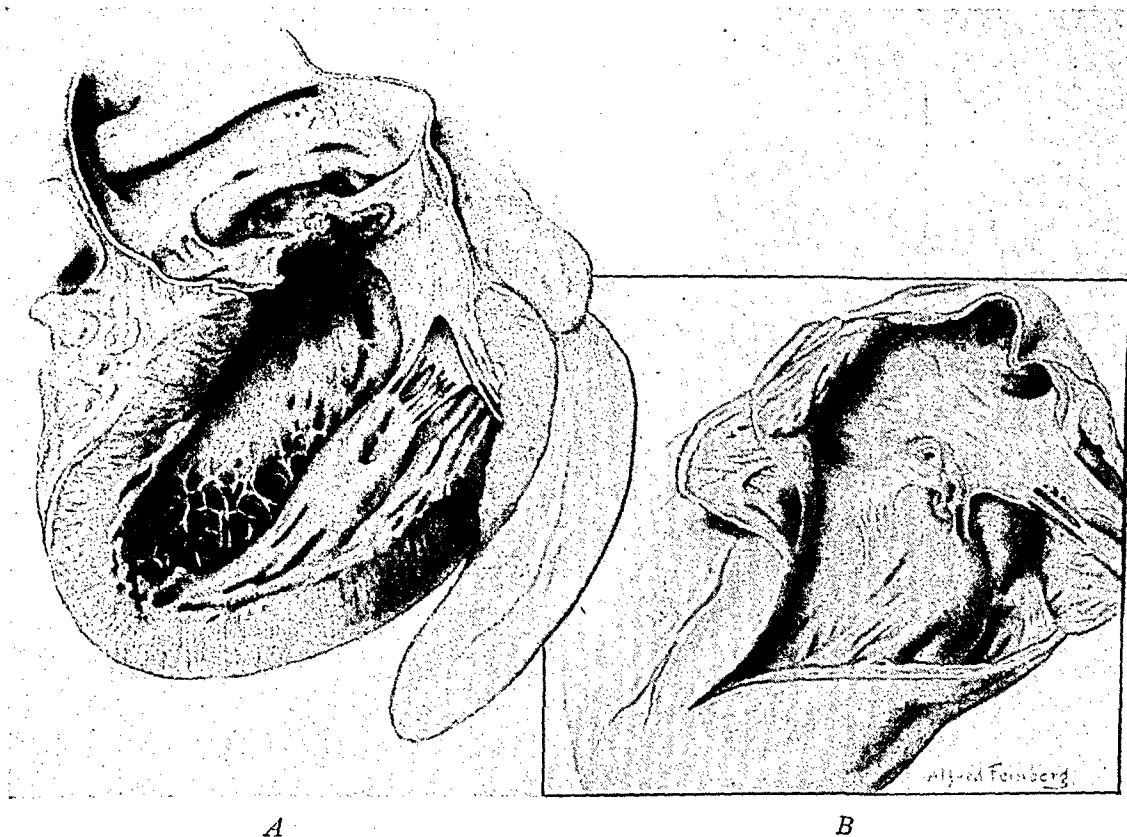


FIG. 1. Drawings of (a) Left heart showing vegetation on bicuspid aortic valve with perforation. Note rolled edges of valve. (b) Right heart showing exit of perforating tract above tricuspid leaflet.

He continued to have chills and fever up to 104° F. Two weeks after admission, tenderness of the nail beds was noticed for the first time, and shortly thereafter innumerable petechiae were present over the entire body including the fundi and oral passages. Stool examinations now gave a positive benzidine reaction. Blood cultures taken in a carbon dioxide atmosphere were reported positive for *Brucella abortus* and the opsonocytophagic reaction was markedly positive. All intradermal allergenic tests, however, were negative. Electrocardiographs showed left axis deviation, regular sinus rhythm and a PR interval varying between 0.19 and 0.23 second. A teleroentgenogram showed marked generalized cardiac enlargement but no typical contour.

The patient's condition became progressively worse. The blood urea fluctuated between 39 and 71 mg. per cent. The specific gravity of the urine during the last

three weeks remained fixed at 1.012. Albuminuria and hematuria were constantly present. No granular casts were ever found. During his course the patient received four transfusions of whole blood. He died suddenly on the thirty-sixth day of hospitalization.

Necropsy Findings: Autopsy was performed six hours after death. The external features were similar to those described clinically.

The heart (figure 1) weighed 620 grams and lay free in the pericardial sac. There was no effusion or evidence of pericarditis. Enlargement externally was mainly left ventricular. When the right auricle was opened the endocardium was found to be smooth and glistening except for a small area just above the anterior cusp of the tricuspid valve where two small perforations were visible. The perforations had

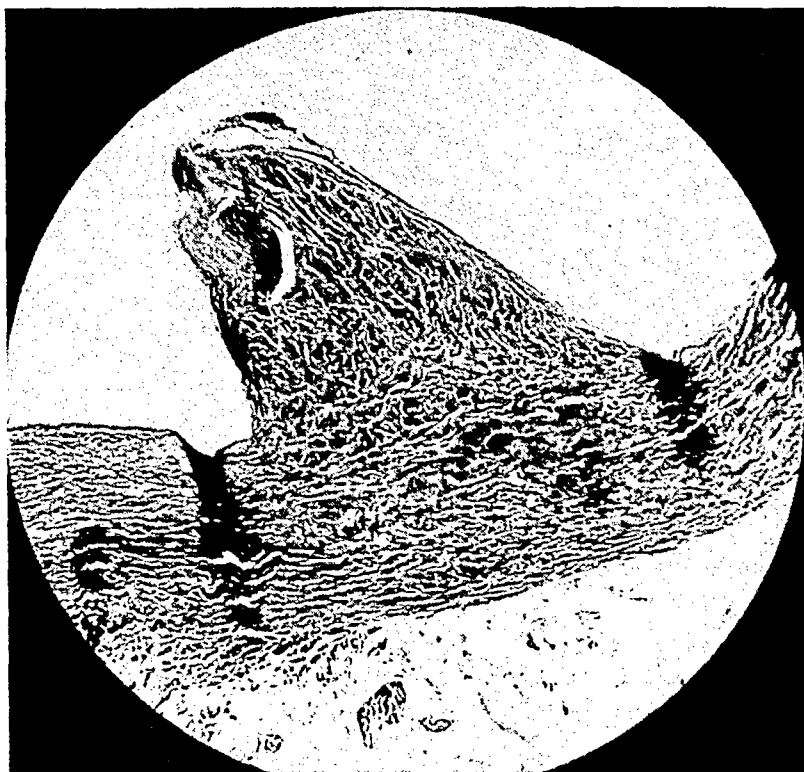


FIG. 2. Photomicrograph of a section of the raphe of the anomalous valve ($\times 15$). Weigert's elastic tissue stain.

friable necrotic edges. The tricuspid valve orifice admitted three fingers and was otherwise normal. The right ventricle and pulmonary valve were not unusual. The left auricle was normal in size and the endocardium smooth and delicate throughout. The orifice of the mitral valve admitted two fingers. The valve leaflets were very thin and delicate as were the chordae tendineae. The left ventricle was markedly hypertrophied and dilated, the wall measuring 2.6 cm. at its thickest part. The aortic valve presented only two cusps, the larger of the two being incompletely divided by a raphe. The width of the larger cusp was smaller than the sum of two normal cusps. A large friable grayish red vegetation measuring 3.5 by 3 cm. partially involved both cusps including the commissure between them. A sinus tract originating in this ulcerative vegetation penetrated through the smaller cusp into the sinus of Valsalva, thence through the base of the aorta and terminated in the right auricle as the perforations described above. The free edges of the aortic cusps were rolled and thickened. The coronary ostia, one arising from behind each cusp, were widely patent as were the coronary arteries. The aorta was otherwise normal except for small atheromata.

The lungs showed merely congestion and edema especially at the bases and posteriorly.

The liver weighed 2660 grams, was deep purplish red in color and extended three fingers' breadth below the costal margin.

The spleen weighed 630 grams, was firm in consistency and extended two fingers' breadth below the costal margin. Three pinkish yellow triangular areas of infarction, the largest measuring three cm. at the base, were present. On section the appearance of infarction was confirmed. In other areas the Malpighian corpuscles were prominent in an otherwise congested pulp.

The adrenals were not unusual.

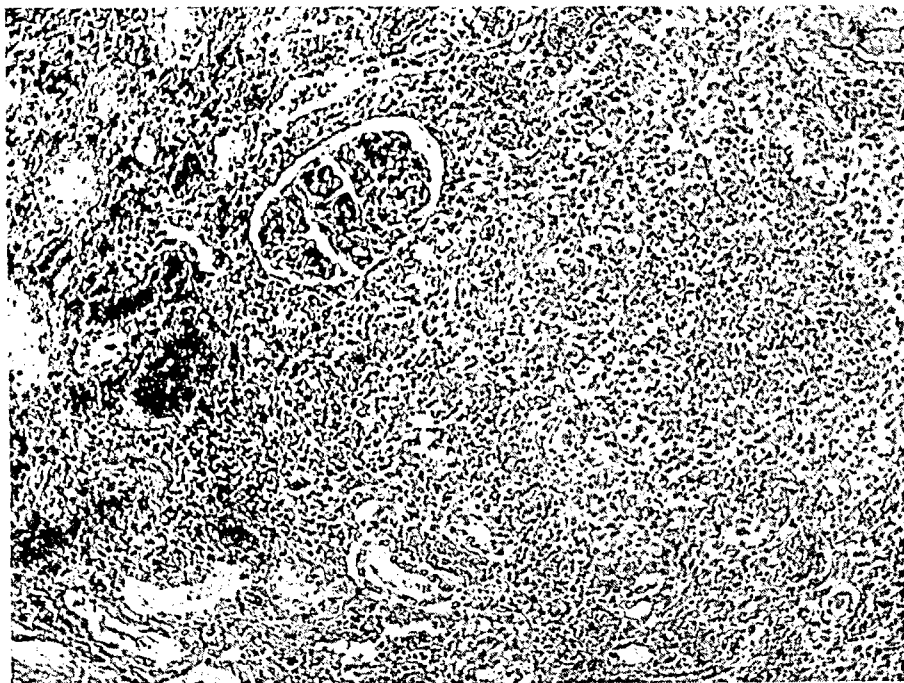


FIG. 3. Photomicrograph of abscess in interstitial tissue of kidney ($\times 75$).
Note normal glomerulus.

The kidneys weighed 360 and 330 grams respectively. The capsules were tense and stripped with slight difficulty. The denuded surface revealed pin-point yellow spots over its entire extent. The demarcation between cortex and medulla was indistinct and the cut surface presented an edematous appearance. The calyces and pelves were normal.

The gastrointestinal tract was not unusual.

Permission for examination of the head was not obtained.

Microscopic Examination: Heart: In the region of the perforation necrosis and acute inflammatory reaction were evident. This reaction was also present on the aortic valve superimposed on which was the vegetation, granular and bluish, and hyalinized in areas with deeply staining areas intermingled between the eosinophilic staining parts. Section of the aorta in the region of the raphe (figure 2) dividing the anomalous valve showed the usual three layers to be present. The endocardium continued uninterrupted over the raphe. The elastic tissue of the media became thinned out as the raphe was approached. The raphe itself consisted of dense hyalin material. The adventitia was not unusual. There was no evidence of any inflam-

matory process either in the form of cellular or vascular reaction. The myocardium showed muscle fiber hypertrophy. There was no evidence of rheumatic involvement.

Congestion and edema were present in the lung sections. In addition were seen conglomerate areas of plasma, round and polymorphonuclear cell infiltration in some of which clear eosinophilic material gave the appearance of necrosis.

The architecture of the liver was well preserved. The central veins and sinusoids were markedly congested with surrounding compression of liver cells.

Sections of the spleen showed the areas of infarction to be well demarcated. The remainder of the splenic tissue showed evidence of acute splenitis and congestion with focal areas of necrosis and cellular infiltrations as were seen in the lung sections.

Kidneys: The main changes were in the interstitial tissue in which areas of polymorphonuclear and round cell infiltration with necrosis were prominent (figure 3). Edema also was present. Scattered glomeruli were atrophic and occasional ones completely degenerate. No endothelial proliferation or crescents were seen. The tubules showed parenchymatous swelling and frequently were filled with clear staining material and occasionally red cells.

Pancreas and adrenals were not unusual.

COMMENT

The infrequency of *B. melitensis* endocarditis has been referred to. The present case is the sixth to be recorded in this country. All except that reported by de la Chapelle have occurred in rheumatic or sclerotic valves. The only finding in his case was a thickened aortic cusp. Our case is the first to be superimposed upon a congenital lesion.

Difficulty in diagnosis may well be a reason for this apparent rarity. All blood cultures taken on routine agar media showed no growth. The first taken in a CO₂ atmosphere showed growth. The diagnosis, however, was entertained after a serum agglutination was done because of the patient's occupation. Skin tests repeated several times were all negative. Opsonocytophagic reaction was markedly positive.⁴ For these reasons it is pointed out that in cases of bacterial endocarditis yielding negative blood cultures on routine media the other diagnostic procedures referred to above be resorted to especially if occupation or pastime suggests the possibility of *B. melitensis* infection.

During the course of this patient's disease it was suggested by one of us that there might be an underlying congenital lesion such as a bicuspid valve. Prolongation of the PR interval has been recorded on numerous occasions^{5, 6, 7} in cases in which bicuspid aortic valve was found at necropsy. The authors have seen one such previous case in which no other pathological abnormality was present either clinically or at necropsy. We realize, however, that this may be coincidental owing to toxic influence on the vagus nerve.

The fact that the patient was told he had heart disease in 1928 is likewise of interest. It would seem that this patient did not have *B. melitensis* endocarditis for 12 years. The only apparent explanation seems to be that he may have had murmurs, especially at the base, arising from a thickening of the aortic cusps resulting from mechanical wear and tear of congenitally imperfect cusps.

The necropsy findings in other viscera of this patient are comparable to those pointed out by de la Chapelle although probably of a more extensive nature. These were possibly on a septicemic basis. Urinary findings ante mortem were not typically those of glomerular nephritis though this was suspected; post

mortem the glomeruli were for the most part spared. Diffuse abscesses have been found in a few cases of undulant fever. The majority show no pathologic changes of the kidney.

Treatment of *B. melitensis* endocarditis has not been a topic of discussion by most authors probably because of its rarity. When mentioned it is in relation to undulant fever in general. In the present instance supportive treatment with blood transfusion was given. Chemotherapy was avoided early because of obvious renal damage and anemia. Later when the diagnosis of endocarditis was confirmed the course was of such short duration that he died before institution of chemotherapy.

SUMMARY

A unique case of *B. melitensis* endocarditis superimposed upon a congenital bicuspid aortic valve is reported. The importance of the various diagnostic procedures is discussed stressing the use of the opsonocytaphagic and serum agglutination tests, and also the use of the CO₂ atmosphere in the isolation of *Brucella abortus* from the blood. The abscess formation in the various viscera and especially in the kidney is pointed out in view of the fact the *Brucella abortus* is usually not considered a pyogenic organism.

REFERENCES

1. SMITH, K. McL., and CURTIS, A. C.: Brucellosis endocarditis, Am. Jr. Med. Sci., 1939, cxcviii, 342.
2. DE LA CHAPELLE, C. E.: Vegetative endocarditis due to the *Brucellus melitensis* with a case report, Am. Heart Jr., 1927, iv, 732.
3. SPINK, W. W., and NELSON, A. A.: Brucellosis endocarditis, ANN. INT. MED., 1939, xiii, 729.
4. HUDDLESON, I. F.: Brucella infections in animals and man, 1934, Commonwealth Fund, New York City.
5. PARKER, R. L., and DRY, T. J.: Coarctation of aorta at unusual site, associated with congenitally bicuspid aortic valve, Am. Heart Jr., 1938, xv, 739.
6. WECHSLER, H. F., and GUSTAFSON, E.: Coarctation of the aorta (adult type); congenital bicuspid aortic valve; subacute bacterial endocarditis, Am. Heart Jr., 1937, xiv, 107.
7. BROTHNER, R. J.: Etiology of hypertension resulting from coarctation of the aorta, Arch. Path., 1939, xxviii, 676.

INFECTIOUS MONONUCLEOSIS AND ENCEPHALOMYELITIS*

By BURTON L. ZOHMAN, M.D., F.A.C.P., and EDMUND G. SILVERMAN, M.D.,
Brooklyn, New York

ONE of the least frequent complications of infectious mononucleosis is involvement of the central nervous system. Because of the fact that a rather careful survey of the literature failed to reveal any case of infectious mononucleosis associated with evidence of diffuse lower motor neurone disease, the following case is herewith reported.

* Received for publication July 23, 1940.

From the Department of Medicine, Israel-Zion Hospital.

CASE REPORT

History. E. N., a young male of 21 years, was admitted to the hospital on January 11, 1940, with a story that he had been taken ill three weeks previously with headache, weakness and fever as high as 103° F. He continued working for about a week but finally on December 28, 1939, went to bed with what appeared to be influenza. During the ensuing week he had pain in the back, general muscular weakness, pain in the inguinal regions, and fever. He was, however, up and about part of the time. By January 6 the weakness of muscles had become very marked and the patient became quite irritable, which was not his usual behavior. On the day before admission, on awakening, the patient found that he was unable to move either his hands or feet. On several occasions irregular twitchings, lasting a few seconds and involving the shoulders, were noted by his mother. He had vomited several times prior to admission as well as on the night of admission. Nothing was noted in the boy's past personal history except that he had had measles, scarlet fever, diphtheria and pneumonia as a child and that he had been operated upon for an undescended testicle 11 years previously. The family history was totally irrelevant.

Physical Examination. The patient, a young male of 21 years, appeared acutely ill. Color was fair. Pupils were equal, reacted equally well to light and accommodation. There was a ptosis of the right upper eyelid. Episcleritis of the left eye was present. The fundi were negative. The nose was negative and there were no points of sinus tenderness. The throat showed several hemorrhagic spots. The tongue deviated somewhat to the left. There was a left peripheral facial paralysis. There were some small glands in the left posterior cervical chain and one large gland in the left submaxillary region. There was slight nuchal rigidity. The lungs were negative. The apex impulse of the heart was felt in the fifth interspace in the nipple line. There was no enlargement to the right or left; the aorta was not widened. The sounds were of good quality, regular in rhythm, of normal rate; there were no accentuations. A soft systolic murmur was audible over the mitral area but it was not transmitted. There was no precordial thrill. The systolic pressure was 146 mm. Hg and the diastolic, 80 mm. Hg. Small axillary glands were palpated bilaterally. The liver dullness extended from the fifth rib to one finger's breadth below the costal margin, although the edge could not be felt. Spleen and kidneys were not palpable. A small umbilical hernia was present. Small inguinal glands were present on the right side, and on deep palpation some small glands in the right lower quadrant of the abdomen could be felt. Dermatographia was present. There was an almost complete flaccid paralysis of all four extremities. The patient was able to move only his fingers and toes. There were fibrillary twitchings of his right arm. No atrophy was noted. All deep reflexes were abolished. There was no disturbance of sensation. The right lower abdominal reflex was active; the right upper and left lower abdominals revealed just a flicker. The right cremasteric reflex was present, the left absent.

A blood study four days prior to admission to the hospital showed a hemoglobin of 100 per cent, a red cell count of 4,650,000 and a white cell count of 12,200 with a differential count of 22 per cent polymorphonuclears of which 17 per cent were non-segmented and 5 per cent segmented forms, 13 per cent lymphocytes, 1 per cent eosinophiles and 64 per cent monocytes. The Westergren index was 10. The heterophile agglutination reaction was positive in dilution of 1:1024. The clinical diagnosis was infectious mononucleosis coupled with a lower motor neurone affection.

Hospital Course. On January 13 a spinal tap was performed. The fluid escaped under an increased pressure of 10 mm. of mercury, was clear, and showed four plus albumin, a faint globulin reaction, four cells per cu. mm. which were lymphocytes, and was negative bacteriologically. The colloidal gold curve and Wassermann re-

actions were negative. A blood count on the same date showed 95 per cent hemoglobin, 5,000,000 red cells, 6800 white cells, with 39 per cent polymorphonuclears of which 15 per cent were nonsegmented and 24 per cent segmented forms, 10 per cent lymphocytes, 35 per cent monocytes, and 16 per cent large lymphocytes. The platelets numbered 210,000. The coagulation time was three and one-half minutes and the bleeding time, four minutes. The blood chemistry was completely normal and the blood Wassermann reaction negative. The urine was also negative.

On January 16 the heterophile reaction was positive in a dilution of 1:512. The blood count showed 98 per cent hemoglobin, 5,280,000 red blood cells, 9250 white blood cells with 48 per cent polymorphonuclears of which 3 per cent were nonsegmented and 45 per cent segmented forms, 3 per cent eosinophiles, 1 per cent basophiles, 25 per cent lymphocytes and 23 per cent monocytes. During the first two days of hospitalization the patient had difficulty in voiding and had to be catheterized. There was also slight difficulty in swallowing during this period. For the next five days there was difficulty in breathing, the respirations at times being shallow. Pains were rather severe and appeared in various parts of the body but mostly in the back and upper extremities. There were marked tremors over the body and marked perspiration, although the patient was afebrile. Speech was of the drawling and nasal type.

An orthopedic consultation on January 16 revealed an inability to elevate either shoulder. Forearms were held in pronation, with inability to supinate. Flexion of elbows was absent, and extension was very weak. There was active motion in the right wrist. Extension of the fingers was restricted; flexion was complete. Findings in the left upper extremity were similar but more marked. The right lower extremity showed no motion about the hip. There was some power in the quadriceps, none in the hamstrings. The foot was held in equinus position. The left lower extremity showed no power in any of the muscles except for a slight trace of dorsiflexion of the left foot.

By January 21 motor power of the right upper extremity had improved considerably, and that of the left to a lesser extent. Movements of both shoulders were better, especially that of the right. There was less ptosis of the right upper eyelid. The patient's speech improved. He was able to wiggle some of the toes of the left foot, and there was slight motion of the extensor tendons of his right foot. The patient had been irrational at times during the previous five days. The neurological examination at this time revealed evidence of diffuse lower motor neurone disease with atrophy of the muscles of the hands, forearms, arms and lower extremities; a nuclear left facial paralysis, deviation of the tongue to the left, fibrillations, impaired palatal function and abnormal involuntary movements including myoclonic and chorea-athetoid movements. The clinical picture implicated the basal ganglia, brain stem and spinal cord and warranted the designation of disseminated encephalomyelitis, most likely of virus origin.

A spinal tap done on January 23 showed the spinal fluid to be under increased pressure, about 60 drops per minute, clear, positive for albumin and positive for glucose. It showed two cells per cu. mm., was negative bacteriologically, and showed a total protein of 68 mg. per cent with a one plus Nonne-Appelt reaction.

On February 6 the patient had developed sufficient power in his back to lift himself up in bed. The left facial paralysis was still in evidence, as was the ptosis of the right upper eyelid, both conditions being less marked. The abdominal reflexes were not obtainable. There was still marked weakness in both upper extremities, the right being weaker than the left. There was fairly good power in both biceps but no power in the triceps. Trapezius muscles were active, as were the pectoralis major and minor muscles. The serratus anticus was weaker on the right but active on both sides. Pronation and supination were weak in both forearms. There was atrophy of

arm, forearm and hands of both upper limbs. Flexion and extension were weak. The flexors of the wrists were very weak and atrophied as well as the thenar and hypothenar eminences. When the fingers were extended, there was hyperextension at the metacarpo-phalangeal joints and slight flexion at the proximal interphalangeal joints. Both lower extremities were paralyzed. There was slight power in the quadriceps on both sides and also in the extensors of the toes. The feet were in slight equinus position.

By March 6 a considerable change had taken place in the patient's condition. The facial paralysis had practically disappeared. He was able to move around in bed, although he could not turn onto his abdomen without assistance. There was a considerable amount of improvement in the upper extremities. He was able to make a fist and could open his hand almost to normal. He was able to turn on the radio and make fine movements with the fingers of his right hand, such as winding his wrist watch. He was able to write. He complained of some numbness of the fingers of both hands, more on the left. He had also developed considerable motor power in his lower extremities. He was able to flex the right knee about half way, to raise the entire right lower extremity in midair for about one minute, and to flex the left knee to a lesser degree.

On March 12 the heterophile reaction had become negative. On March 16 bilateral horizontal nystagmus was noted. There was still evidence of left nuclear facial palsy. There was no tremor nor were there any uncontrolled movements of the upper extremities. There was greater strength in the back musculature, and the patient was partially able to sit up. Speech was normal. Motor power in all extremities had returned to a remarkable degree, but the left upper and lower extremities still revealed appreciable impairment. Generalized muscular atrophy especially of the interossei of both hands and of the muscles of the calves, was evident. A moderate left foot drop persisted. The right lower abdominal reflex was active, the others sluggish. The right cremasteric reflex was present and the left was barely elicited. All deep reflexes were greatly diminished. There was no ataxia, but there was some overpointing in the finger to nose test of the left hand. There was no Babinski reflex, no ankle clonus, no sensory change.

On March 20 the patient was discharged after having been able to sit up in a chair for the preceding three days. He felt much stronger generally and really had no complaint other than his motor incapacity. Although motor power had been restored in all extremities to a very marked degree, there was still some weakness of the left upper and lower extremities as compared with the right, a difference of about 30 per cent; otherwise, the physical findings were those noted on March 16. A blood count taken on March 22 showed a hemoglobin of 97 per cent with 5,780,000 red blood cells, 6850 white blood cells, and a differential of 50 per cent polymorphonuclears, 2 per cent eosinophiles, 1 per cent basophiles, 40 per cent lymphocytes, and 7 per cent monocytes.

Treatment was essentially supportive, coupled with the use of thiamin chloride parenterally in doses of 10,000 units three times daily for a period of about a month. This was followed by the oral use of vitamin B₁, 5 mg. daily, and by suitable orthopedic measures to prevent deformity as well as adequate physiotherapeutic measures.

Hecht Johansen³ in 1931 first described a case of infectious mononucleosis complicated by encephalomeningitis. In 1931, Epstein and Dameshek⁴ likewise reported a case of glandular fever with serous meningitis. Fledelius⁵ in 1935 described a case of mononucleosis in the course of which a partial ocular motor paralysis took place, probably owing to an encephalitic process. He assumed that the encephalitis was brought about by the same agent which caused the infectious mononucleosis with its accompanying anginal symptoms. Sucher

and Schwarz¹⁴ in 1936 reported a case of infectious mononucleosis complicated by encephal meningitis, with mild right oculomotor paresis as well as left upper extremity paresis. Gsell,⁹ in 1937, reported five cases of infectious mononucleosis, three of which were cases associated with acute serous meningitis and two with secondary facial paralysis which appeared as the main illness was on the decline. In 1938, Huber⁷ reported a case of glandular fever complicated by hyperesthesia of the skin of both feet and a spinal fluid showing a pleocytosis of 333 cells, mostly lymphocytic elements, and a protein increase to 110 mg. per cent.

The etiology of infectious mononucleosis is not definitely known. The first impetus to a study of the problem was given by Murray, Webb and Swann¹⁰ in 1926, who isolated *Bacterium monocytogenes*, apparently belonging to the group of *Listerella*, from rabbits having a generalized infection associated with an increase in the number of large mononuclear lymphocytes. Bland,^{1,2} in 1931, inoculated rabbits with the blood of patients at the height of the disease and then isolated a protozoan of the genus *Toxoplasma* from the rabbits, and believed that this was the cause of the disease. This could not be confirmed by other investigators.

Stimulated by these findings many workers began to look for a microbe in human patients. Nyfeldt,¹¹ in 1929, reported the isolation from the blood of an organism which he called *Bacterium monocytogenes hominis* and with which he produced the cellular blood picture in rabbits. Schmidt and Nyfeldt,¹² in 1938, reported five cases of infectious mononucleosis which were admitted to the hospital either with an angina or a peritonsillar abscess. One case, in addition, showed on admission clear signs of meningitis, whereas the other four, after having been afebrile for from two to 11 days, developed signs of meningitis and a spinal fluid indicative thereof, i.e., containing 6 to 138 cells per cu. mm. The blood culture in all five cases showed a growth of an organism of the *Listerella* group, one after four days, a second after six days, and three after 21 days. The spinal fluid also showed a similar growth; in the first case after six days, in the second case after nine days, and in the other three after 9, 11 and 21 days.

Soon doubt appeared as to the etiological significance of the *Listerella* group of organisms in the production of infectious mononucleosis, first because many observers had failed to confirm the isolation of the *Listerella* organism, and secondly because it had been recovered from the spinal fluid of cases afflicted with meningoencephalitis without any relation to infectious mononucleosis. Caspar Burn,³ for example, grew *Listerella* from the blood of three newborn infants who had died in the New Haven Hospital from meningoencephalitis. Schultz, Terry, Brice and Gebhardt¹³ isolated *Listerella* from spinal fluid of a nurse who was suddenly taken ill with fever, headache, stiffness of neck, doubtful Kernig sign, strabismus, ptosis of left eyelid, diplopia, facial twitch and lethargy. The spinal fluid was cloudy with 812 cells, 95 per cent of which were small lymphocytes. A rabbit inoculated intracerebrally with 0.5 c.c. of the spinal fluid developed a severe encephalitis two days after inoculation. The same organism was cultivated from the brain tissue of this animal.

McKinlay,⁹ in 1935, in a study of 50 cases of infectious mononucleosis, found that repeated blood cultures were all negative and that emulsions of fresh glandular substance made during the acute stages and injected into monkeys and

guinea pigs were without demonstrable effect. It would thus seem that the *Listerella* group of organisms are secondary invaders or contaminations.

During the past year, some very interesting experiments which would point to a virus etiology have been performed. They have consisted for the most part of an attempt to transfer the disease to monkeys by means of lymph gland material from patients with infectious mononucleosis. Wising¹⁷ summarizes his results as follows: "Fresh lymph gland obtained from two patients with infectious mononucleosis and injected into macacus monkeys, produced after 8 and 18 days, mild clinical symptoms with general lymphadenitis and a slight increase in the mononuclear cells of the blood. These changes could be reproduced in monkeys by injection of an emulsion from an extirpated lymph gland, in the one case in five passages, in the other case, in two. An assistant who, at the operation on monkey "Passage 3," pricked his finger with the knife which had just been used to divide the extirpated monkey lymph gland, felt ill the same day as monkey "Passage 4" with symptoms which appeared to be typical of infectious mononucleosis. All the author's attempts to isolate microorganisms from the blood of the patients taken during the initial febrile stage and from the affected lymph glands of both man and monkey, were unsuccessful.

Likewise, Van den Berghe and Liessens^{15, 16} in 1939 inoculated a *Macacus rhesus* subcutaneously with the blood of a child having infectious mononucleosis and produced a syndrome which was characterized by lymphocytosis, leukopenia and a positive heterophile reaction. After filtering through a Seitz filter blood from patients with infectious mononucleosis, the authors succeeded in reproducing the disease in successive passages from monkey to monkey and this they did on many occasions. They concluded, therefore, that they were dealing with a filterable virus. They further attempted to culture the virus in tissue and were able, by means of a special medium consisting of a suspension of pieces of chicken embryos minced in Tyrode's fluid together with 10 per cent human serum, to preserve not only the virulence of the virus but to increase it by successive subculture.

It is common knowledge that some of the viruses have affinities for the central nervous system, and a number of diseases such as poliomyelitis, rabies and encephalitis are the result of the neurotropic properties of these viruses. On the other hand, many virus diseases such as measles and variola which usually do not show any affection of the central nervous system, in a few rare cases are complicated by encephalitis and myelitis. We may, therefore, assume that some viruses which usually have an affinity for organs other than the nervous system, in some cases may acquire neurotropic properties. It is further reasonable to conclude that in some cases of infectious mononucleosis the virus may also acquire neurotropic properties. In view of these facts, it seems to us that our case, which was characterized not only by a blood picture of infectious mononucleosis but also by a neurological picture of encephalomyelitis, was caused by one virus with neurotropic properties rather than by two different viruses.

SUMMARY

1. A case of infectious mononucleosis with diffuse lower motor neurone disease in a man of 21 years, with recovery, is reported.

2. The literature of infectious mononucleosis complicated by involvement of the cerebrospinal nervous system is reviewed.

3. Recent experimental evidence supporting the theory that infectious mononucleosis is caused by a filterable virus is presented.

BIBLIOGRAPHY

1. BLAND, J.: Discussion on glandular fever, *Proc. Roy. Soc. Med.*, 1931, xxv, 135-177.
2. BLAND, J. O. W.: Glandular fever. II. The protozoal nature of the experimental disease, *Brit. Jr. Exper. Path.*, 1931, xii, 311-319.
3. BURN, CASPAR G.: Unidentified gram-positive bacillus associated with meningo-encephalitis, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxi, 1095-1097.
4. EPSTEIN, SAMUEL H., and DAMESHEK, WILLIAM: Involvement of central nervous system in a case of glandular fever, *New England Jr. Med.*, 1931, ccv, 1238-1241.
5. FLEDELIUS, M.: Case of mononucleosis with paralysis of ocular muscles, *Acta Ophth.*, 1935, xiii, 150-152.
6. GSELL, O.: Serous meningitis with infectious mononucleosis, *Deutsch. med. Wchnschr.*, 1937, lxiii, 1759-1762.
7. HUBER, W.: Serous meningitis in Pfeiffer's glandular fever, *Schweiz. med. Wchnschr.*, 1938, lxviii, 892-893.
8. JOHANSEN, A. H.: Serous meningitis and infectious mononucleosis, *Acta med. Scand.*, 1931, lxxvi, 269-272.
9. MCKINLAY, C. A.: Infectious mononucleosis, *Jr. Am. Med. Assoc.*, 1935, cv, 761-764.
10. MURRAY, E. G. D., WEBB, R. A., and SWANN, M. B. R.: Rabbits' disease caused by bacillus *Bacterium monocytogenes*, *Jr. Path. and Bact.*, 1926, xxix, 407-439.
11. NYFELDT, A.: Etiologie de la mononucleose infectieuse, *Compt. rend. Soc. de biol.*, 1929, ci, 590-592.
12. SCHMIDT, VIGGO, and NYFELDT, AAGE: Infectious mononucleosis and meningo-encephalitis, *Ugesk. f. laeger*, 1938, c, 336-339.
13. SCHULTZ, E. W., TERRY, M. C., BRICE, A. T., JR., and GEBHARDT, L. P.: Bacteriological observations in case of meningo-encephalitis, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxi, 1021-1023.
14. SUCHER, A., and SCHWARZ, E.: Lymphatische Reaktion und Encephalo-meningitis, *Wien. klin. Wchnschr.*, 1936, xlix, 1417-1424.
15. VAN DEN BERGHE, L., LIESSENS, P., and KOVACS, L.: Transmission of human infectious mononucleosis to *Macacus rhesus*, *Compt. rend. Soc. de biol.*, 1939, cxxxi, 156-158.
16. VAN DEN BERGHE, L., and LIESSENS, P.: Transmission de la mononucleose infectieuse au *Macacus rhesus* et passages successifs d'un virus filtrant, *Compt. rend. Soc. de biol.*, 1939, cxxx, 279-283.
17. WISING, J.: Experiments with lymph gland material from cases of infectious mononucleosis, *Acta med. Scand.*, 1939, xcvi, 328-339.

UVEOPAROTITIS; CASE REPORT *

By MARIE L. CARNS, M.D., F.A.C.P., *Madison, Wisconsin*

UVEOPAROTITIS (uveo-parotid fever or Heerfordt's syndrome) is a comparatively rare condition. Approximately 100 cases have been reported in the literature, the majority in Scandinavian and German journals of ophthalmology. No

* Received for publication July 26, 1940.

From the Department of Medicine, University of Wisconsin.

previous case has been so diagnosed at the Wisconsin General Hospital. The essential features are bilateral inflammatory lesions of the uveal tract and bilateral parotitis, often associated with paralyses of the cranial nerves, usually the peripheral portion of the seventh. The parotitis is of a chronic almost painless type, with a tendency to progress to resolution without suppuration. A low grade fever is generally present. The ocular manifestations commonly follow the glandular swelling, but may precede it or occur concomitantly. Usually the facial paralysis, when it occurs, follows the parotitis, but occasionally it, too, precedes or occurs simultaneously. In some cases the lacrimal, submaxillary and sublingual glands have also been involved. The majority of cases which have been reported have occurred in the second and third decades, but it may occur at any age. It is somewhat more prevalent in females and in the white race.

Uveoparotitis, as a clinical syndrome, was first recognized in 1909 by the ophthalmologist Heerfordt of Copenhagen.¹ He expressed the belief that the disease was an atypical form of mumps. Since that time many different etiologic factors have been proposed. The majority of clinicians and pathologists seem now to be of the opinion that tuberculosis is the primary factor. The case for a tuberculous etiology was well presented by Garland and Thomson in 1933.² They even termed the condition "uveo-parotid tuberculosis." They state that in no case in which a biopsy was performed was histologic evidence of tuberculosis lacking. Some observers, on the other hand, are opposed to the theory of tuberculosis as the cause of the condition. This opposition is based on the results of animal inoculations and tuberculin tests which are more often negative than positive, and on the clinical observation that these patients seldom show the more common symptoms or signs of tuberculosis. It does not lie within the scope of this report to enter into any detailed discussion of this controversial point, but inasmuch as Dr. Max Pinner very kindly reviewed the biopsy from the parotid gland in this case and has written several articles on noncaseating tuberculosis within the past few years, a brief résumé of his conclusions on the subject will be presented.³ He states that from a study of the literature it seems quite likely that so-called uveo-parotid fever belongs in the general classification of non-caseating tuberculosis. Boeck's sarcoid, osteitis tuberculosea multiplex cystoides, certain cases of Mikulicz's syndrome, and a number of disseminated pulmonary and lymph node lesions would also be included. He points out that clinically, noncaseating tuberculosis is a rather benign chronic disease, showing a certain tendency to intermittence and recurrence. Histologically, as far as material is available, there "is not only uniformity but monotony" in regard to the lesions. Biologically it is of interest to note that a large percentage of these patients with noncaseating tuberculosis, as far as they were tested, reacted only slightly or not at all to tuberculin. (However, Pinner feels that this is apparently not the anergy of the non-infected organism, since in a respectable number of patients it was possible to show that they have tuberculin neutralizing substances, anticutines, in their serum.) He summarizes the circumstantial and indirect evidence for the etiological nature of this group of diseases as follows: (1) The histological characteristics of the lesions. (2) The demonstration of anticutines and therewith of positive tuberculin anergy. (3) The fact that practically all patients who expired died of frank tuberculosis.

Our patient, a 36-year-old married white female, was first admitted to the Medical Service of the Wisconsin General Hospital on September 20, 1938. Her chief complaint was swelling of the parotid glands bilaterally. She had felt perfectly well until about three months previously, at which time she had contracted a severe "cold." She had driven with the car window open, exposing the left side of her face to a draft. The muscles of the left face suddenly became paralyzed. She next noticed sore eyes. A diagnosis of iritis was made at a local clinic and she was treated with typhoid vaccine. The facial paralysis gradually improved. About five weeks before



FIG. 1.

admission tonsillectomy was performed. Within 48 hours the patient noted tender swellings in front of the ears, associated with marked dryness of the mouth. The height of the swelling occurred about four weeks before admission, since which time there had been a gradual decrease of the bilateral parotid enlargement and a progressive increase in the amount of saliva present.

Inventory by systems added only photophobia and a 25-pound weight loss in the past three months. Past history established the occurrence of bilateral mumps four years ago. Social and family histories were non-contributory. There was no known tuberculosis in the family.

Physical examination showed a well nourished woman of the pyknic type. There was evident enlargement of the parotid glands bilaterally, the left being considerably larger than the right (figure 1). The enlarged parotid glands were firm and non-tender. The submaxillary glands were moderately enlarged, but were not of so firm a consistency as the parotids. The upper eyelids showed slight edema, but there was no enlargement of the lacrimal glands; the extraocular movements were normal; there was slight circumcorneal injection of each eyeball. The pupils were dilated and fixed (atropine had been used daily previous to admission). The irides lacked their normal clearness. The fundi were not abnormal. An ophthalmologist reported the presence

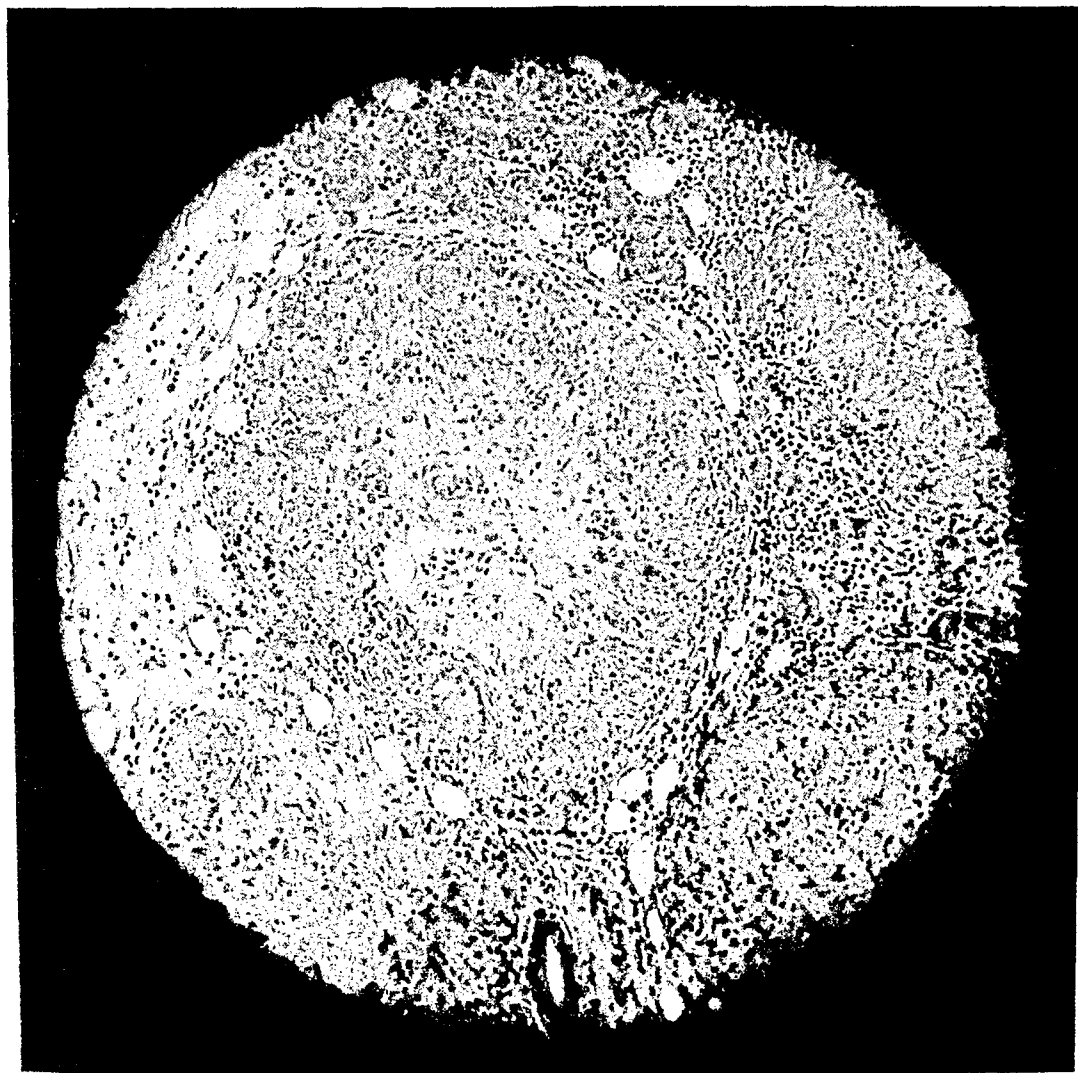


FIG. 2.

of keratitis punctata on the left, believed to be in Descemet's membrane. There was slight facial asymmetry, with a decreased nasolabial fold on the left, but no residual facial paralysis. A thyroidectomy scar was present. Blood pressure was 100 mm. Hg systolic and 76 mm. diastolic. The tip of the spleen was just palpable on deep inspiration. The highest temperature recorded during her 25-day hospitalization was 99.8° F. The usual range was 98° to 99.2° F.

Laboratory studies showed hemoglobin 15 grams, red blood cells 4,700,000, white blood cells 5,038, with 71.6 per cent neutrophils, 2.6 per cent eosinophiles, 0.4 per cent basophiles, 14.2 per cent small lymphocytes, 3 per cent large lymphocytes, 7 per

cent monocytes, 0.6 per cent large young cells, and 0.6 per cent unclassified cells. The blood Wassermann reaction was negative. Spinal fluid showed protein 54 mg. per cent, sugar 53 mg. per cent, gold sol 1221100000, Ross Jones and Noguchi reactions faintly positive and one cell per cu. mm. Chest roentgen-ray showed no evidence of recent or active parenchymal infiltration. There was no evidence of any osseous disease in the skull, spine or right femur. Biopsy of the left parotid gland showed the gland largely replaced by epithelioid hyperplasia and tubercle formation. A few atypical giant cells were seen. There was considerable lymphocytic infiltration (figure 2). A section was sent to Dr. Max Pinner, who concurred in the diagnosis of



FIG. 3.

noncaseating tuberculosis. A Mantoux test with 0.01 mg. old tuberculin was negative, but positive with 1.0 mg.

On the advice of consultants from the Chest and Radiologic Services, the patient received three radiations of 150 r. each over the left parotid on alternate days. There was no immediate adverse or favorable reaction. She also received vitamins A, C and D in excess of those contained in an adequate diet. The uveitis was treated with 1 per cent atropine b.i.d., warm compresses t.i.d., and 5 per cent dionin at night.

At the request of the radiologic consultant she returned in December 1938. At this time there was no evidence of the previous parotid swelling (figure 3). The submaxillary lymph glands had decreased in size but remained just palpable. An

ophthalmologist considered her eyes "greatly improved" but advised further observation. There were no symptoms referable to the eyes at this time. The tip of the spleen remained palpable. The blood count and sedimentation rate were within normal limits. A roentgenogram of the chest showed no change. There was no temperature elevation above 99° F. during her eight-day hospitalization. She was again given three radiations of the same dosage as previously, over the left parotid gland.

During the following 14 months the patient was examined at intervals in the Out-patient Department. All symptoms and signs progressively diminished to complete disappearance. Further irradiation of the parotid and treatment of the eyes were not deemed necessary. She was last admitted to the hospital in February 1940. She returned at this time at our request for complete progress studies. She stated that she felt perfectly well. She had gained 18 pounds in weight. The eyes were considered entirely normal on this occasion. No residuals of the previous extensive changes were determined. It is of interest that at this time she had a positive Mantoux test with 0.01 mg. of old tuberculin.

The prognosis in this disease is generally conceded to be good as to life and fair as to residua. Only four deaths have been reported in the literature, and of these, three were due to miliary tuberculosis.⁴ There is usually no permanent impairment of the general health, and the parotitis and nerve paralyses almost invariably disappear. There may be permanent impairment of visual acuity, however, and recurrences of the uveitis, even ultimately resulting in blindness, are not uncommon.

Inasmuch, then, as this condition usually undergoes spontaneous resolution, one must obviously be very guarded in giving any particular form of treatment too much credit for a "cure."

SUMMARY

A case of uveoparotitis, a comparatively rare affection, is presented. The etiology, course, treatment and prognosis are briefly discussed.

REFERENCES

1. HEERFORDT, C. F.: Über eine "Febris uveo-parotidea subchronica," Arch. Ophth., 1909, lxx, 254-273.
2. GARLAND, H. G., and THOMSON, J. G.: Uveo-parotid tuberculosis, Quart. Jr. Med., 1933, xxvi, 157-177.
3. PINNER, MAX: Non cascating tuberculosis, Am. Rev. Tuberc., 1937, xxxvi, 706-709; 1938, xxxvii, 690-728; 1939, xxxix, 186-203.
4. MICHELSON, H. E.: Uveoparotitis, Arch. Dermat. and Syph., 1939, xxxix, 329-344.
5. FOLGER, H. P.: Uveoparotitis, Arch. Ophth., 1936, xv, 1098-1116.
6. ARBUSE, D., and MADONICK, M.: Uveo-parotid fever (Heerfordt's syndrome); neurologic manifestations; report of two cases, Am. Jr. Med. Sci., 1938, cxvii, 222-232.

CHRONIC MENINGOCOCCEMIA COMPLICATED BY ACUTE ENDOCARDITIS *

By ROBERT B. NYE, M.D., F.A.C.P., CHARLES W. SEMISCH, III, M.D., and
LOUIS MERVES, M.D., *Philadelphia, Pennsylvania*

THE etiological agent of epidemic cerebrospinal meningitis, the meningococcus, was first described in 1887 by Weichselbaum. Gwyn¹ demonstrated the meningococcus in the blood stream. W. W. Herrick, who has had a very extensive experience with meningococcic infections, divided the infection into three stages, viz: (1) local invasion of the upper respiratory tract, (2) invasion of the blood stream, (3) metastatic localization. It is the consensus of opinion at present² that in the pathogenesis of epidemic cerebrospinal meningitis, the pathway of infection is via blood stream rather than by direct extension from the nasopharynx, and that the process may terminate at any stage, the latter fact being attested to by the increasing number of meningococcemias reported in recent years without any localizing manifestations.

In our review of the American literature we have chosen 69 cases of chronic meningococcus septicemia and have excluded those cases of the so-called "Waterhouse-Friderichsen syndrome" (acute fulminating meningococcic septicemia with bilateral adrenal hemorrhages).

Chronic meningococcemia without meningitis was first reported in Germany by Solomon in 1902.³ Since then there have appeared sporadically in the literature presentations of similar cases. Carbonell and Campbell⁴ critically reviewed the literature to 1938 and accepted 30 cases to which they added three of their own. The three cases which they observed were treated with anti-meningococcic serum and all recovered. The septicemia was complicated by meningitis in 42.4 per cent of the cases, endocarditis in 12.1 per cent, with a total mortality rate of 9.1 per cent.

At about this time Appelbaum⁵ collected 15 cases in the Bellevue Hospital in New York. Of these, 46 per cent developed meningitis, 20 per cent endocarditis; the total mortality rate for this series was 13.3 per cent. He noted that blood culture rarely was positive until the third week of the disease, and stated that the patient's serum does not as a rule agglutinate meningococci.

Since then there have appeared further reports. Krusen and Elkins⁶ presented a case of chronic meningococcemia and associated endocarditis which was treated with fever therapy and intravenous prontosil with recovery. Willius and Eaton⁷ observed a case of chronic meningococcemia complicated by endocarditis with death despite intensive serum therapy. Heinle⁸ presented five cases with three deaths. Of these, two were complicated by endocarditis, and the third, after a 14 year history of recurrences, finally succumbed to cerebral hemorrhage. The two patients who recovered were treated with antiserum and with meningococcus vaccine respectively. Binns and Clancy⁹ reported two cases cured by sulfanilamide. Goundry and Phalen¹⁰ successfully treated one case with serum. Rosenbluth and Stetten¹¹ reported a case of meningococcic septicemia complicated by meningitis. The meningitis subsided with serum

* Received for publication August 2, 1940.

From the Department of Therapeutics, Jefferson Medical College Hospital.

therapy, but the septicemia persisted. Fever therapy was administered with complete recovery. Zendel and Greenberg¹² reported two cases, the first of which was treated with antitoxin, antiserum and sulfanilamide. The second was treated with sulfanilamide alone. Both cases recovered. Top and Young¹³ treated one case with antitoxin (Ferry) which was found to be ineffective. Antiserum was then given with complete success. Schwentker, Gelman and Long¹⁴ treated one case with sulfanilamide with recovery. Hennell and Weiner¹⁵ observed a case of chronic meningococcemia complicated with endocarditis which resulted in death. Long and Bliss¹⁶ reported five cases treated with sulfanilamide with recovery.

TABLE I

Author	No. cases observed	No. deaths	Autopsy
Gwyn.....	1	1	Yes
McMahon and Burkhart.....	1	1	Yes
Rhodes.....	1	1	Yes
Warfield and Walker.....	1	1	Yes
Cecil and Soper.....	1	1	Yes
Finley and Rhea.....	1	1	Yes
Hennell and Weiner.....	1	1	No
Krusen and Elkins.....	1	0	Recovery
Willius and Eaton.....	1	1	Yes
Heinle.....	2	2	No
Masters.....	3	0	Recovery
Hyland.....	1	1	Yes
Appelbaum.....	3	0	Recovery
	18	11	
Authors' case.....	1	1	Yes
	19	12	

Incidence of endocarditis 27.1 per cent.
Mortality rate when complicated by acute endocarditis 63.2 per cent.

In table 1 are listed the cases of endocarditis complicating meningococccic septicemia. In the seven cases of endocarditis which recovered the etiology is doubtful, as there was a history of rheumatic infection and abnormal heart sounds in several instances. Further than this, it is a fact that fever and anemia may produce cardiac murmurs without any demonstrable structural change. The case report presented is noteworthy in that there is no previous history of heart damage. At the onset of the present illness the heart appeared to be normal by physical examination and by electrocardiograms.

CASE REPORT

G. W., male, white, aged 20, had been discharged from this hospital two years previously with a diagnosis of diabetes mellitus and balanoposthitis. One month prior to admission, following a seashore excursion, he awakened with a severe head cold and pain in the right ear. After two days his family doctor was consulted; he found the patient suffering with a discharge from the right ear, cough with expectoration, and slight fever. His ear was treated intermittently for two weeks and the discharge ceased. A week prior to admission he awakened with chills, vomited, and within a few hours had a high fever and profuse sweats. The following day he com-

plained of marked malaise and first noted the appearance of "red spots" over the entire body. The family doctor was again consulted, a diagnosis of acute rheumatic fever was made, and treatment was carried out on that basis. Chills and fever continued, joint pains developed, the red spots persisted, and hospitalization was advised. He was admitted to the medical service on September 7, 1939, complaining of chills and fever, arthralgia and myalgia, and a generalized eruption of a week's duration.

On physical examination the patient was a young athletic male who appeared acutely ill. The ears grossly were normal. There was photophobia. The pharynx was injected, the tonsils enlarged and inflamed. Examination of the lungs was negative. The heart was normal in size and position; no abnormalities of rhythm or heart sounds were detected. Abdominal examination was negative. There was no swelling or redness of the joints, but they were tender and painful on motion, the pain being more marked in the third toes of both feet. There were numerous small subcutaneous swellings throughout both extremities that were painful and not well circumscribed. There was a generalized maculopapular, pustular, violaceous eruption, which did not blanch on pressure; the only parts of the body free from these lesions were the palms of the hands and the hairy regions. The temperature was 100 $\frac{3}{4}$ ° F., pulse rate 94, respiratory rate 22, blood pressure 116 mm. Hg systolic and 64 mm. diastolic, hemoglobin 84 per cent, red blood cells 4,200,000, white blood cells 9,600, color index 1.0, neutrophils 80 per cent, lymphocytes 18 per cent, myelocytes 2 per cent. Urine examination was negative; blood sugar was 51 milligrams per 100 c.c. The diagnostic possibilities considered at this time were: one of the infectious fevers, acute rheumatic fever, bacterial endocarditis, tuberculosis, malaria, and chronic meningococcemia.

Laboratory Findings: Wassermann and Kahn tests were negative. Weil-Felix reaction was negative. Agglutination and skin tests for undulant fever were negative. Gonococcic complement fixation test was negative. No plasmodia were found in the blood smears. Stool studies were negative for typhoid bacilli. Seven consecutive blood cultures were negative until October 12 (five weeks after admission), at which time the meningococcus was recovered, there being less than five colonies per cubic centimeter. Spinal fluid examinations were negative on three occasions. Blood coagulation studies and platelet count were normal. The roentgenologic study of the chest on September 18 was reported as probable acute tracheobronchitis with the possibility of Hodgkin's disease. On September 20 roentgen-ray of the ear regions showed chronic mastoiditis on the right side with possible activity.

Course: Since an etiological diagnosis was not possible at first, treatment was symptomatic. On September 28 an accentuated first sound was heard at the mitral area. The spleen was questionably palpable. It was noted that as the rash disappeared the temperature dropped several degrees. The otologist reported contraction and thickening of the right tympanic membrane. On October 9 a diastolic murmur at the mitral area was noted, and later a systolic murmur developed. The patient complained of occasional bouts of pain in the left hypochondrium. At no time were red blood cells, albumin, or casts noted in the urine. At this time bacterial endocarditis was the tentative diagnosis. A course of sulfapyridine therapy was begun on October 6, the first positive blood culture being obtained on October 12, six days later. A specimen of the culture was sent to Dr. Sara Branham at the U. S. Public Health Service for typing. Sulfapyridine was continued, and because a satisfactory blood level was not being secured, on October 22, 10 grams of sodium sulfapyridine were given intravenously in a liter of physiological salt solution. A maximum blood concentration of 9.1 milligrams per 100 cubic centimeters of blood was secured at this time. The agglutination titer of the patient's serum against the organisms isolated by blood culture and against a known strain of meningococcus was 1:160 on October 18.

On October 28 the patient's condition became critical. For the first time his diabetes presented a serious problem. The patient was uncoöperative and refused nourishment. Blood culture on October 30 was positive for meningococcus, with 200 colonies per cubic centimeter. The hemoglobin and red blood cells had dropped. On October 29 the agglutination titer had dropped to 1:40, and serum therapy was started with polyvalent antimeningococcic serum. The following day the patient developed



FIG. 1. Arrow indicates vegetation on mitral valve.

signs of fluid in the right hemithorax. Thoracentesis was done and 4 c.c. of cloudy fluid obtained which yielded no growth. Roentgen-ray examination of the chest at this time revealed an extensive atypical pneumonia, and a probable bilateral pleural collection of fluid.

On November 1 the patient was in a semistuporous state. Blood sugar was 400 milligrams, carbon dioxide combining power was 36, non-protein nitrogen 68. The

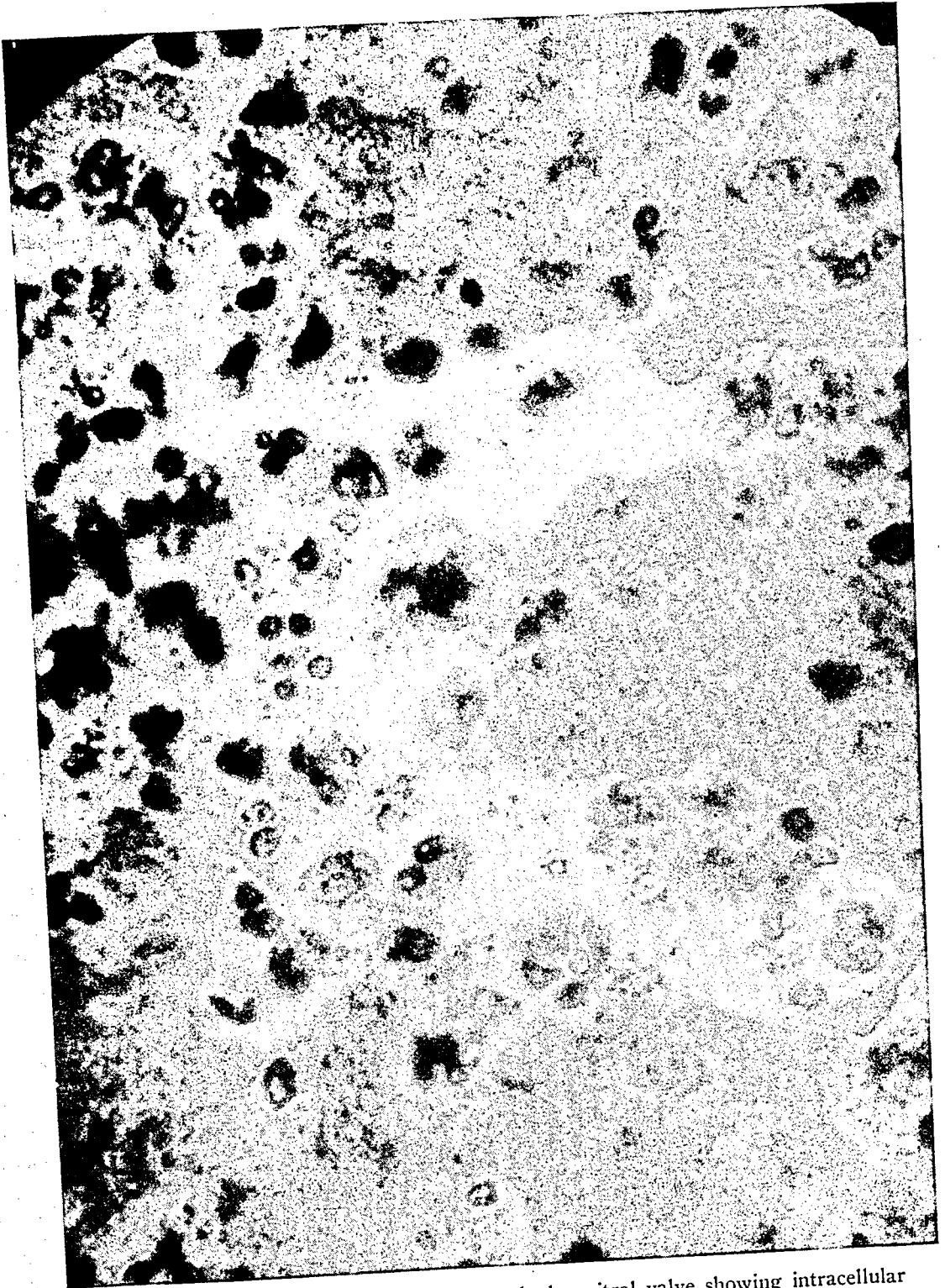


FIG. 2. Microphotograph of section through the mitral valve showing intracellular diplococci ($\times 1200$).

only significant electrocardiographic finding was reported on November 1, at which time there was a tachycardia and a diphasic T-wave in LIVCF-3. Transfusions were given on November 1, 2, and 3, of 500 c.c. of citrated whole blood. On November 2 the U. S. Public Health Service reported *Meningococcus* Type II. A new lot of serum which was particularly high in type II antibodies was secured and its intravenous administration begun. At this time the agglutination titer determination was incomplete agglutination at 1:40. The patient seemed better, although his temperature and pulse showed no significant change. On November 5, 1939, the patient suddenly died.

Autopsy Findings: There were small pericardial and peritoneal effusions. The heart weighed 360 grams. The epicardial surface was smooth, moist and glistening. On the atrial surface of the anterior mitral leaflet there was a large vegetation which measured approximately three centimeters at its base. It was firmly adherent and around its edges the endocardial lining revealed definite ulceration (figure 1). The remaining valve cusps were normal. An acute ulcerative and vegetative endocarditis

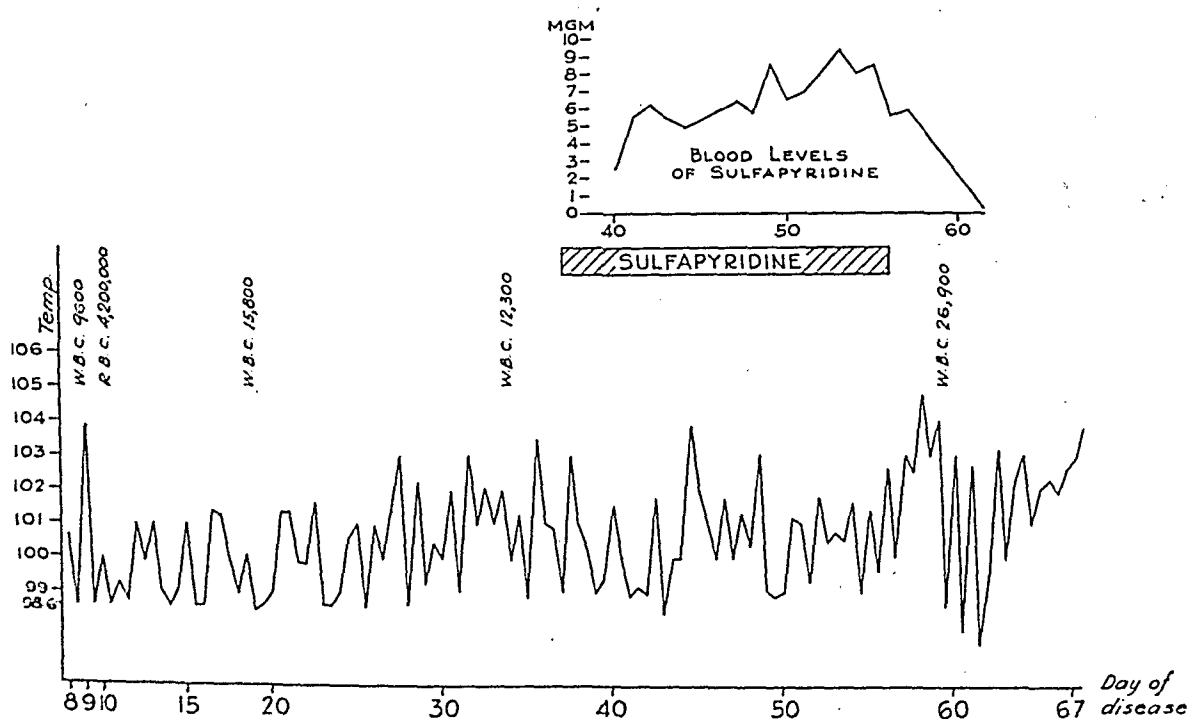


FIG. 3. Graph showing temperature curve, representative leukocyte counts, and sulfapyridine levels.

of the mitral valve was present. In sections made through the mitral valve, bean-shaped diplococci were seen within the cytoplasm of the polymorphonuclear leukocytes (figure 2). Multiple infarcts of the spleen and kidney were demonstrable. There was partial atelectasis of the right lung. There was no evidence of meningitis. The only abnormal finding in the brain was a small area of softening in the rostral portion at the base of the pons.

DISCUSSION

Chronic meningococcemia is a disease entity characterized by (1) intermittent chills, fever and sweats, (2) maculopapular rash occurring in crops, (3) myalgia and arthralgia, (4) moderate polymorphonuclear leukocytosis, (5) positive blood cultures, usually not obtained before the third week, and (6) variable

duration of one to 30 weeks, though in one of the cases reviewed (Heinle, *supra* vide) there is a history of recurrences extending over 14 years.

Herrick¹⁷ states that the two most serious and most frequently occurring complications of meningococcic sepsis are meningitis and endocarditis, and that in the latter the lesions are usually present on the mitral and aortic valves. The disease runs an acute or subacute course and almost always ends fatally. This is fully borne out by the autopsy findings in the cases noted.

In the present case sulfapyridine administration was begun six days before the first positive blood culture was obtained. When the literature was reviewed it was learned that Dimson¹⁸ and Hobson and McQuaide¹⁹ had treated meningococcic infection successfully with M & B 693, and on this basis sulfapyridine was continued. Despite adequate therapeutic dosage, no beneficial effect was observed, and the disease progressed. When the agglutination titer of the patient's serum dropped, antiserum was given intravenously, with little hope and no expectation of preventing a fatality in the face of the already established bacterial endocarditis.

We believe that in this case sulfapyridine was given a fair trial, and that it did not influence the course of the disease. It obviously did not prevent the localization in the mitral valve area.

Polyvalent antiserum was given late in the illness. It is an accepted fact that it reduces the mortality rate in epidemics of meningococcic meningitis from 70 per cent to between 11 per cent and 30 per cent (Topley and Wilson²). In view of the proved efficiency of the antiserum we believe it should be used in meningococcic infection as soon as an etiological diagnosis has been made.

Insofar as the use of sulfanilamide in conjunction with serum therapy is concerned, the work of Branham and Rosenthal²⁰ on experimental animals would indicate a synergistic action, the combined effect being greater than either component alone. Waghelstein²¹ studied a series of 106 patients suffering from meningococcic infections to determine the value of sulfanilamide. Seventy-two were treated with sulfanilamide, yielding a mortality rate of 12 per cent, whereas the mortality in the 34 cases treated with serum and sulfanilamide was 13 per cent. These results compare favorably with the experience of those who used serum alone in epidemics of meningitis. It would seem, theoretically at least, that the use of bacteriostatic agent (sulfanilamide) combined with a specific antibacterial serum is highly desirable.

CONCLUSIONS

1. The American literature is reviewed and a case reported of chronic meningococcemia complicated by endocarditis, proved by bacteriologic and post-mortem findings.

2. The mortality of meningococcic sepsis complicated by endocarditis in the cases to date is 63 per cent.

3. It would seem that the rational procedure in the treatment of this disease would be the use of sulfanilamide and antiserum, type specific where possible.

4. The disease entity is sufficiently characteristic clinically to warrant bedside diagnosis.

BIBLIOGRAPHY

1. GŴYN, N. B.: A case of general infection by the *Diplococcus intracellularis* of Weichselbaum, Bull. Johns Hopkins Hosp., 1899, x, 112-113.
2. TOPLEY, W. W. E., and WILSON, G. S.: Principles of bacteriology and immunity, 2nd Edition, 1936, William Wood and Co., Baltimore, page 1127.
3. SOLOMON, H.: Über Meningokokkenseptikämie, Berl. klin. Wchnschr., 1902, xxxix, 1045.
4. CARBONELL, A., and CAMPBELL, E.: Prolonged meningococcemia, Arch. Int. Med., 1938, lxi, 646.
5. APPELBAUM, E.: Chronic meningococcus septicemia, Am. Jr. Med. Sci., 1937, cxciii, 96.
6. KRUSEN, F. H., and ELKINS, E. C.: Fever therapy for gonococcemia and meningococcemia with associated endocarditis, Proc. Staff Meet. Mayo Clin., 1937, xii, 324.
7. WILLIUS, F. A., and EATON, L. M.: Clinic on meningococcemia with vegetative mitral endocarditis (subacute bacterial endocarditis); with findings at postmortem examination, Proc. Staff Meet. Mayo Clin., 1937, xii, 762.
8. HEINLE, R. W.: Meningococcic septicemia, Arch. Int. Med., 1939, lxiii, 575.
9. BINNS, F., and CLANCY, J. J.: Chronic meningococcemia promptly cured by sulfanilamide, Am. Jr. Dis. Child., 1939, lvii, 404.
10. GOUNDRY, F. W., and PHALEN, T. H.: Meningococcemia without meningitis, New York State Jr. Med., 1937, xxxvii, 491.
11. ROSENBLUTH, M. B., and STETTEN, D.: Meningococcus septicemia treated by fever therapy, New York State Jr. Med., 1938, xxxviii, 1078.
12. ZENDEL, J. F., and GREENBERG, D.: Meningococcemia, treatment with sulfanilamide and prontosil, New York State Jr. Med., 1937, xxxvii, 1744.
13. TOP, F. H., and YOUNG, D. C.: Continued fever, meningococcemia, Jr. Michigan State Med. Soc., 1938, xxxvii, 528.
14. SCHWENTKER, F., GELMAN, S., and LONG, P. H.: The treatment of meningococcic meningitis with sulfanilamide, Jr. Am. Med. Assoc., 1937, cviii, 1407.
15. HENNEL, H., and WEINER, H. J.: Report of a case of chronic meningococcemia, Med. Jr. and Rec., 1930, cxxxi, 292.
16. LONG, PERRIN, and BLISS, ELEANOR: Clinical use of sulfanilamide and sulfapyridine and allied compounds, 1939, page 188, Macmillan Co., New York.
17. HERRICK, W. W.: Meningococcic sepsis, Cecil's Text Book of Medicine, Fourth Edition, 1937, W. B. Saunders Co., Philadelphia, page 199.
18. DIMSON, S. B.: Chronic meningococcal septicemia treated with 2-(p-Aminobenzene-sulphonamido) pyridine, Lancet, 1938, ii, 424.
19. HOBSON, F. G., and McQUAIDE, H. G.: Treatment of meningococcal meningitis with 2-Sulphanilyl-Amidopyridine (M & B 693), Lancet, 1938, ii, 1213.
20. BRANHAM, S. E., and ROSENTHAL, S. W.: Sulfanilamide, serum, and combined drug and serum in the therapy of experimental meningococcic and pneumococcic infections in mice, Pub. Health Rep., 1937, lii, 685.
21. WAGHELSTEIN, J. M.: Sulfanilamide in the treatment of 106 patients with meningococcic infections, Jr. Am. Med. Assoc., 1938, cxi, 2172.

EDITORIAL

SOME INDICATIONS AND CONTRAINDICATIONS FOR SPLENECTOMY

THE spleen has long been known to include among its functions an important rôle in the production of the formed elements of the blood and also in their eventual elimination from the circulation. These functions are dependent primarily upon the reticuloendothelial cells in the spleen, and they are shared in varying degree by other organs and tissues which contain such cells. In the normal adult the part which the spleen plays directly in contributing new cells to the circulation is insignificant and is limited probably to the production of a few lymphocytes and monocytes. In certain types of anemia, however, particularly those in which bone marrow is displaced or destroyed, compensatory active extramedullary hematopoiesis often occurs. This may involve any of the types of blood cells, and in it the spleen usually plays a prominent part.

Under normal conditions the spleen in common with other reticuloendothelial tissues is actively concerned with the removal of cells from the circulation, largely by phagocytosis. The part it plays in the removal of red blood cells is well established. It is generally believed that platelets are similarly removed. It is also likely that various types of leukocytes are taken up and destroyed in the spleen, although the number so disposed of is probably insignificant compared with those which migrate into or are excreted into the lumen of the gastrointestinal and respiratory tracts. Normally this process is presumably limited to the removal of aging or defective cells. At least the rate of removal and the rate of cell production are so nicely adjusted that only slight fluctuations occur in the number of circulating cells.

Under pathological conditions, however, the rate of cell destruction may be so accelerated that a serious cell deficiency develops. This is well established in the case of the red cells in familial hemolytic jaundice, and in the case of the platelets in essential thrombocytopenic purpura. There is still a question as to whether this depends primarily upon a defect in the cells resulting from faulty production, or upon a pernicious overactivity of the spleen. That the degree of activity is excessive from the standpoint of the welfare of the patient is shown by the excellent clinical results which follow splenectomy, quite regularly in familial hemolytic jaundice and frequently in essential thrombocytopenic purpura.

Hitherto little attention has been paid to the possibility of an analogous disturbance in which the leukocytes are primarily destroyed. In 1938, however, Wiseman and Doan¹ in a preliminary report described three cases

¹ WISEMAN, B. K., and DOAN, C. A.: A newly recognized granulocytopenic syndrome caused by excessive splenic leukolysis and successfully treated by splenectomy, *Jr. Clin. Invest.*, 1939, xviii, 473.

which apparently fit into such a category, and in this number of the ANNALS OF INTERNAL MEDICINE they are reporting five such cases in detail under the designation "primary splenic neutropenia." These cases complained chiefly of weakness, fever, and coryza or angina. They showed a marked leukopenia and granulocytopenia together with a progressive enlargement of the spleen. Leukemia and ordinary malignant neutropenia were excluded by examining aspirates of sternal marrow, which showed active hyperplasia involving chiefly the neutrophilic myelocytes. The spleens in all cases were removed and showed an extraordinary ingestion of neutrophilic leukocytes by the splenic phagocytes. In some cases the presence of anemia and of thrombocytopenia and bleeding indicated that this hyperactivity of the spleen is not necessarily restricted to the leukocytes, but may extend also to the red cells and platelets.

The view of Wiseman and Doan that the spleen is primarily at fault receives support from the great rapidity with which the leukocyte count rose after operation, often reaching normal a few hours after the splenic pedicle was ligated. It is also supported by the sustained clinical improvement observed in all these cases after splenectomy. Furthermore one patient subsequently survived a severe attack of erysipelas and showed a normal leukocytic response to the infection. The importance of recognizing such cases early and giving them the benefit of splenectomy is obvious, in view of the futility of other methods of treatment. As these authors point out, however, a precise diagnosis is essential before resorting to such a radical procedure.

The successful results usually obtained by splenectomy in these diseases as well as in occasional cases of acquired hemolytic jaundice and Banti's syndrome have led in some clinics to the indiscriminate use of the operation in cases of refractory anemia of obscure origin. In some cases, as in unrecognized leukopenic leukemia, the operation is dangerous and futile, and in some it is positively harmful. Aside from the immediate risk from the operation, the greatest direct injury is inflicted on those cases whose splenic enlargement is owing to a compensatory extramedullary hematopoiesis. Radiation, if effective, is similarly harmful. Splenic hyperplasia of this type may occur in some severe hemolytic anemias, such as Cooley's Mediterranean anemia, in which the bone marrow, although hyperplastic, is unable to keep pace with the rate of cell destruction. It is seen most commonly, however, in the myelophthitic anemias, in which the marrow cells are injured or crowded out by various foreign tissues. In addition to the well known conditions which give rise to anemias of this type, there is a group of obscure origin which run a chronic course and are often mistaken for chronic myeloid leukemia because of the changes in the blood. There is a severe anemia and a marked leukocytosis with many myelocytes and normoblasts, and often cells even more primitive in type. Some cases, however, have been mistaken for Hodgkin's disease, Banti's disease, and even neoplasms of the spleen.

Cases of this type have been reported under many different terms; for example by Hickling² as "chronic non-leukemic myelosis," and by Vaughn and Harrison³ as myelosclerosis. Ten such cases have been described by Jackson et al.⁴ and more recently five others by Reich and Rumsey⁵ as "agnotogenic myeloid metaplasia of the spleen." As Jackson has pointed out, an accurate diagnosis requires not only a thorough physical examination and a study of the blood but also an adequate examination of the sternal marrow and the spleen.

The marrow in these cases has not shown any constant characteristic changes, but it is not leukemic. In some cases the cells have been replaced in varying degree by fibrous tissue and even by new bone. Roentgenograms of the bones, however, are often normal, even in the presence of fibrosis, and in some cases the marrow has been described as normal or hyperplastic. The distinctive feature is the occurrence of areas of hematopoiesis in the spleen. In some cases material obtained by puncture may suffice for diagnosis, but in others an actual biopsy of both organs may be required. The necessity for an accurate diagnosis is indicated by the fact that many of these 15 cases were subjected to splenectomy or radiation, and all were injured by these measures. The anemia was aggravated, transfusions were required more frequently, and in some death was manifestly hastened.

Splenectomy is invaluable in saving life and restoring health in properly selected cases in which the diagnosis is established. On the other hand it is a very dangerous procedure to use blindly as a measure of last resort. It should not be employed unless there is a positive indication for its use, and it should be deferred until all possible means have been taken to exclude diseases in which it is useless or harmful. Examination of the marrow is often required to accomplish this, and sometimes also of the spleen.

² HICKLING, R. A.: Chronic non-leukemic myelosis, *Quart. Jr. Med.*, 1937, vi, 253-275.

³ VAUGHN, J. M., and HARRISON, C. V.: Leukoerythroblastic anaemia and myelosclerosis, *Jr. Path. and Bact.*, 1939, xlviii, 339-352.

⁴ JACKSON, H., PARKER, F., JR., and LEMON, H. M.: Agnogenic myeloid metaplasia of the spleen. A syndrome simulating other more definite hematologic disorders, *New England Jr. Med.*, 1940, ccxxii, 985-994.

⁵ REICH, C., and RUMSEY, W., JR.: Agnogenic myeloid metaplasia of the spleen, *Jr. Am. Med. Assoc.*, 1942, cxviii, 1200-1204.

REVIEWS

Nutritional Deficiencies; Diagnosis and Treatment. By JOHN B. YOUMANS, A.B., M.S., M.D., assisted by E. WHITE PATTON, M.D. 385 pages; 23.5 × 16 cm. J. B. Lippincott Co., Philadelphia. 1941. Price, \$5.00.

This volume is offered not as a treatise on deficiency diseases for the dietitian or investigator, but as a reliable source of information for the busy physician, bringing to him in an orderly manner the essential basic facts gleaned from an exhaustive study of the existing literature concerning the clinical manifestations of these disorders.

Only those facts directly applicable to man are included, and such work as may be still called controversial has been omitted. Particular attention is devoted to the recognition and treatment of the principal avitaminoses. Iron and iodine deficiency is also thoroughly discussed, the more uncommon mineral deficiencies being briefly covered.

Each chapter is well organized and clearly written. Footnotes have been omitted. References are few but well chosen. An appendix containing methods of laboratory diagnosis, and a tabular summary of the vitamins with principal dietary sources are given. Illustrations are few but appropriate.

To the internist or general practitioner this book can be recommended as a means of arriving at an intelligent solution of the problem of the treatment of the avitaminoses without recourse to the voluminous literature on these subjects.

J. W.

Diseases of Metabolism. Edited by GARFIELD G. DUNCAN, M.D. 985 pages; 17 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1942.

In his preface to this work the Editor discusses the problems of presentation of a book on metabolism and outlines his aim as an attempt "to provide for the physician a practical basis for the understanding, diagnosis and treatment of the various metabolic disorders." There can be no doubt that he has been most successful in presenting a well organized, interesting and complete volume.

The first five chapters discuss metabolism of carbohydrate, protein, lipids and minerals, and are written by G. G. Duncan, C. N. H. Long, Abraham White, and Abraham Cantarow. Water balance is next treated by J. P. Peters, nutritional and metabolic aspects of diseases of the blood by L. M. Tocantins, and vitamins and avitaminosis by T. D. Spies and H. R. Butt. Chapters on undernutrition and obesity are written by L. H. Newburgh and Frank A. Evans, xanthomatosis by E. Mason, gout by Bauer and Klemperer, and diabetes insipidus and diseases of carbohydrate metabolism by G. G. Duncan and A. Cantarow.

It is impossible, in a short review, to do justice to a work of such character and merit. The reviewer believes that it can be fully recommended.

T. N. C.

Immunology. By NOBLE PIERCE SHERWOOD, Ph.D., M.D., F.A.C.P., Professor of Bacteriology, University of Kansas, and Pathologist to The Lawrence Memorial Hospital, Lawrence, Kansas. Second edition. 639 pages; 15.5 × 23.5 cm. C. V. Mosby Co., St. Louis. 1941. Price, \$6.50.

Published first in 1935, the second edition of this textbook gives evidence of careful revision. Much old material has been removed and the results of recent investigations have been incorporated. This has occasionally required the rewriting of whole sections. New chapters have been added on the reticulo-endothelial system and serum sickness. Many transpositions of material have been made, both within and among

chapters. This has led to greater continuity of thought and clarity of presentation. The illustrations on the whole are helpful and the references appended to each chapter are adequate. The total impression gained is that the book has been greatly improved and should be of value to medical and other students interested in immunology and serology.

F. W. H.

Handbook of Communicable Diseases. By FRANKLIN H. TOP, A.B., M.D., M.P.H., and collaborators. 682 pages; 23.5 × 15.5 cm. C. V. Mosby Co., St. Louis. 1941. Price, \$7.50.

This is an interesting book which one thoroughly enjoys. Reading this handbook is a pleasure for many reasons, among which are its large print, its unity and coherence, and its concise information.

The whole book is extremely well organized. Diseases are classified according to the common portal of entry, and the descriptions of the individual diseases follow a uniform plan. Specific nursing care is stressed for each of the different infections. The illustrations are splendid.

Dr. Top's book seems to be more than just a handbook, since it contains such a wealth of material without being too detailed, and yet it is written in a flowing, interesting style.

W. M. S.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of Publications by Members are gratefully acknowledged.

Books

- Dr. Lewellys F. Barker, F.A.C.P., Baltimore, Md.—“Time and the Physician”;
Dr. Edward L. Hanes, F.A.C.P., Webster, N. Y.—“The Minds and Nerves of Soldiers”;
Dr. Edward B. Krumbhaar, F.A.C.P., Philadelphia, Pa.—“A History of Medicine” (a translation from Arturo Castiglioni);
Dr. Herbert Pollack, F.A.C.P., New York, N. Y.—“Modern Diabetic Care”;
Dr. Albert H. Rowe, F.A.C.P., Oakland, Calif.—“Elimination Diets and Patient’s Allergies.”
Dr. Abraham Rudy, F.A.C.P., Boston, Mass.—“Simplified Diabetic Manual”;
Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis.—“Vitamin Therapy in General Practice.”

Reprints.

- Walter M. Bartlett, F.A.C.P., Captain, (MRC), U. S. Army—1 reprint;
J. Edward Berk (Associate), Lieutenant, (MRC), U. S. Army—1 reprint;
Dr. John A. Foley, F.A.C.P., Boston, Mass.—1 reprint;
Dr. John Harvey, F.A.C.P., Lexington, Ky.—1 reprint;
Dr. John Harlan Hornbaker, F.A.C.P., Hagerstown, Md.—2 reprints;
Dr. Cullen Ward Irish, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—2 reprints;
Dr. Estelle E. Kleiber, F.A.C.P., New Brunswick, N. J.—2 reprints;
Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—2 reprints;
Frank B. Queen, F.A.C.P., Major, (MRC), U. S. Army—1 reprint;
Dr. John W. Scott, F.A.C.P., Lexington, Ky.—3 reprints;
Dr. Thornton Scott (Associate), Lexington, Ky.—4 reprints;
Dr. Walter Wessels, F.A.C.P., Los Angeles, Calif.—2 reprints;
Dr. Willard R. Wirth, F.A.C.P., New Orleans, La.—1 reprint.

Dr. Samuel Johnston, F.A.C.P., Toronto, Ont., was elected President of the Academy of Medicine of Toronto at its 35th Annual Meeting on May 5, 1942. The Academy’s Fellowship numbers 1198, of whom about 16 per cent are on active military service. The Academy is helping to provide medical libraries for overseas medical units recruited from the Toronto district. Its local library now contains more than thirty thousand volumes.

Dr. Clifford W. Mack, F.A.C.P., Livermore, Calif., was elected President of the Society of Neurology and Psychiatry of Northern California at its last meeting, April 19, 1942.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "Nutrition as It Applies to General Disease," illustrated by a motion picture in natural color, at a meeting of the Lehigh County Medical Society in Allentown, Pa., May 12, 1942.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., presented a paper on "Liver Therapy and Vitamin-B Complex in Cirrhosis of the Liver and Atrophic Gastritis" at the 176th Annual Meeting of the State Medical Society of New Jersey, Section on Gastroenterology, held in Atlantic City. Dr. Harold S. Davidson, F.A.C.P., Atlantic City, led a discussion on this paper.

Dr. Fred M. Meixner, F.A.C.P., Peoria, Ill., has been reelected President of the Illinois Tuberculosis Association and elected a member of the Board of Governors of the Mississippi Valley Conference on Tuberculosis.

On May 19, 1942, Dr. Meixner presented a paper entitled "The Tuberculous Obstetric Patient," at the meeting of the Illinois Medical Society in Springfield.

The 15th Graduate Fortnight of the New York Academy of Medicine will be held October 12-23, 1942. The subject of this Fortnight will be "Disorders of the Nervous System," and the program will include morning panel discussions, afternoon clinics, evening lectures, scientific exhibits and demonstrations. Among the Fellows of the College who will participate in the evening lectures at this meeting will be:

Dr. Edward A. Strecker, Philadelphia, Pa.—"Military Psychiatry";
Dr. Harold G. Wolff, New York, N. Y.—"The Emotions and Disease";
Dr. Walter Freeman, Washington, D. C.—"Prefrontal Lobotomy."

Dr. Robert Lyle Motley, F.A.C.P., Memphis, Tenn., was one of the guest speakers at the Fifth Councilor District meeting of the Arkansas Medical Society held recently in El Dorado. Dr. Motley spoke on "Diagnosis of Digestive Disturbances and Their Physiologic Explanation."

Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., spoke on "Diseases of the Heart Amenable to Surgical Treatment" at the annual meeting of the California Medical Association held in Del Monte, May 4-7, 1942.

At a joint clinical conference of the Missouri and Illinois Post-Graduate Committees held in Belleville, Ill., April 9, 1942, Dr. Francis J. Braceland, F.A.C.P., Chicago, Ill., spoke on "Psychiatry—Recognition of the Psychopathic State in the Selectee."

The Medical and Chirurgical Faculty of the State of Maryland held its 144th Annual Meeting in Baltimore, April 28-29, 1942. Among the speakers on the program were:

Dr. Thomas Nelson Carey, F.A.C.P., Baltimore, Md.—"Rocky Mountain Spotted Fever";

Dr. Thomas P. Sprunt, F.A.C.P., Baltimore, Md.—"Blood Plasma Proteins";

Leon A. Fox, F.A.C.P., Colonel, (MC), U. S. Army—"The Doctor in War."

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., delivered one of the Trimble Lectures on "Syndromes Associated with Leukopenia."

Among the guest speakers at the 74th Annual Meeting of the Nebraska State Medical Association held in Omaha, May 4-7, 1942, were:

Dr. Henry W. F. Woltman, F.A.C.P., Rochester, Minn.—"Postoperative Neurologic Complications";

Dr. Benjamin Goldberg, F.A.C.P., Chicago, Ill.—"The Present Day Tuberculosis Problem";

Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill.—"Bedside Neurology for the General Practitioner";

Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.—"Endocrine Problems in the Male."

The South Dakota State Medical Association held its 61st Annual Meeting in Sioux Falls, May 13-15, 1942. At this meeting Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn., spoke on "The Treatment of the Patient Over Fifty," and Dr. Herbert Z. Giffin, F.A.C.P., Rochester, Minn., discussed "Iron, Liver Extract and Vitamins in the Treatment of Various Types of Anemia."

Under the Presidency of Dr. Neil D. Buie, F.A.C.P., Marlin, Tex., the State Medical Association of Texas held its 76th Annual Session in Houston, May 11-14, 1942. Among the guest speakers were:

Leonard G. Rowntree, F.A.C.P., Colonel, (MRC), U. S. Army—"Medical Aspects of Selective Service";

Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala.—"Diagnosis of Deficiency Diseases";

Dr. John H. Musser, F.A.C.P., New Orleans, La.—"The Heart that Grows Old."

Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif., spoke on "Tuberculosis—The General Practitioner's Problem" at a meeting of the King County (Wash.) Medical Society at Seattle, March 16, 1942.

Dr. George W. McCoy, F.A.C.P., New Orleans, La., spoke on "Tropical Medicine: Scope and Achievements," and Dr. Guy H. Faget, F.A.C.P., U. S. Public Health Service, Carville, La., spoke on "The Story of Leprosy in the United States," at a symposium on Tropical Medicine conducted at the annual meeting of the Medical Library Association in New Orleans, May 7-9, 1942.

The American Association of the History of Medicine held its 18th Annual Session in Atlantic City, N. J., May 3-5, 1942, under the Presidency of Dr. Jabez H. Elliott, F.A.C.P., Toronto, Ont., Canada. Among the speakers at this meeting were:

Dr. Ernest E. Irons, F.A.C.P., Chicago, Ill.—"Théophile Bonet";

Dr. Maurice S. Jacobs, F.A.C.P., Philadelphia, Pa.—"Thomas Beddoes and His Contribution to the Treatment of Tuberculosis."

At the dinner meeting, May 4, Dr. Elliott delivered the presidential address on "Observation and Interpretation."

Under the Presidency of Dr. James H. Means, F.A.C.P., Boston, Mass., the Association of American Physicians held its 57th Annual Meeting in Atlantic City, N. J., May 5-6, 1942. Among the speakers were:

Dr. Harold W. Jones, F.A.C.P., Dr. Leandro M. Tocantins (Associate), and Dr. Lowell A. Erf (Associate), Philadelphia, Pa.—"Concentrated Blood Plasma, Intrasternally, in the Treatment of Shock";
Dr. Ralph A. Kinsella, F.A.C.P., St. Louis, Mo.—"Hyposthenia";
Dr. Roy W. Scott, F.A.C.P., and Dr. Curtis F. Garvin (Associate), Cleveland, Ohio—"Unusual Cardiac Mechanism Associated with Metastatic Cancer Involving the Left Auricle";
Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.—"Chorionic Gonadotropin: A Potent Stimulator of Growth."

Dr. Edwin E. Osgood, F.A.C.P., Portland, Ore., discussed "The General Principles of Chemotherapy" at the 106th Semi-annual Meeting of the Southern California Medical Association held in Riverside, April 10-11, 1942.

The Annual Alumni Clinic Day of Wayne University College of Medicine, Detroit, Mich., was observed May 6, 1942. Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., spoke on "Proved Preparations in Endocrine Therapy and Their Application," and Dr. John T. Murphy, F.A.C.P., Toledo, Ohio, spoke on "X-Ray Treatment of Lesions of the Face."

The New Hampshire Medical Society held its 151st Annual Session in Manchester, May 12-13, 1942. Dr. Paul D. White, F.A.C.P., Boston, Mass., conducted a symposium on "Heart Disease," and round table conferences were conducted by Dr. Ernest E. Irons, F.A.C.P., Chicago, Ill., on "Aspiration Pneumonia," and Dr. William Halsey Barker (Associate), Baltimore, Md., on "Recent Development in Therapy with Sulfonamide Drugs."
Dr. Irons also spoke at the Society's banquet. The subject of his address was "The Last Illness of Sir Joshua Reynolds."

On March 10, 1942, Dr. Reginald Fitz, F.A.C.P., Boston, Mass., spoke on "Clinical Aspects of Jaundice" at a meeting of the Broome County Medical Society at Binghamton, N. Y.

The 89th Annual Session of the Medical Society of the State of North Carolina was held in Charlotte, May 11-13, 1942. Among those who participated in the program were:

Dr. Paul D. White, F.A.C.P., Boston, Mass.—"Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease";
Henry C. Coburn, Jr., F.A.C.P., Brigadier General, (MC), U. S. Army—"The Responsibility of the Civilian Physician in the War Emergency";

Dr. Mark A. Griffin, F.A.C.P., Asheville, N. C.—“The Treatment of Chronic Alcoholism”;

Dr. Archibald A. Barron, F.A.C.P., Charlotte, N. C.—“Experience and Treatment of Certain Mental and Nervous Disorders by Prefrontal Lobotomy.”

Dr. Walter R. Johnson, F.A.C.P., Asheville, N. C., was awarded the Moore County Medal for the best paper read at the Society's 1941 Session. The subject of this paper was “Is Diverticulitis of the Colon a Surgical Disease?”

Dr. Benjamin E. Clarke, F.A.C.P., Providence, R. I., spoke on “The Blood Bank—A General Discussion” at a recent meeting of the Rhode Island Society of Pathologists in Woonsocket.

At a recent meeting of the Medical Society of Humacao (P. R.) County, a symposium on “Consideration of Injuries and Disabilities in Connection with Hostile Aircraft Attacks on Civilian Population” was conducted. Among the speakers were: Drs. Luis Manuel Morales, F.A.C.P., Juan A. Pons, F.A.C.P., Ramon M. Suarez, F.A.C.P., and Federico Hernandez Morales (Associate), all of San Juan.

Dr. Paul D. White, F.A.C.P., Boston, Mass., was elected President of the American Heart Association at its recent meeting in New York, N. Y. Among the other officers of the Association are: Dr. Roy W. Scott, F.A.C.P., Cleveland, Ohio, Vice President; Dr. T. Homer Coffen, F.A.C.P., Portland, Ore., Treasurer; and Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio, Secretary.

Dr. Jerome E. Andes, F.A.C.P., Tucson, Ariz. was one of the speakers at the recent annual meeting of the Arizona Public Health Association. Dr. Andes spoke on “Chemical Substances Occasionally Introduced into Food by Accident.”

Dr. J. Burns Amberson, Jr., F.A.C.P., New York, N. Y., spoke on “What to Do with Tuberculosis Discovered by Case Finding” and “Features of the Early Pulmonary Infiltration,” at the annual session of the California Tuberculosis Association held in Los Angeles, April 9–11, 1942. Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill., spoke on “Applications of Our Knowledge of Pathogenesis of Tuberculosis to Case Finding.”

Among the guest speakers at the 83rd Annual Session of the Kansas Medical Society held in Wichita, May 11–14, 1942, were:

Dr. Alan Brown, F.A.C.P., Toronto, Ont., Canada—“Feeding Difficulties Encountered in the Newborn Period”;

Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa.—“Modern Therapy in Cardiology”;

Dr. Paul A. O'Leary, F.A.C.P., Rochester, Minn.—“Modern Treatment of Syphilis”;

Dr. Cyril M. MacBryde (Associate), St. Louis, Mo.—“Synthetic Estrogens and Their Use.”

Dr. Irvin R. Fox, F.A.C.P., Eugene, Ore., has been reappointed a member of the State Board of Medical Examiners.

Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass., delivered the 8th Edwin A. Jarecki Lecture at the Jewish Hospital, Philadelphia, Pa., April 23, 1942. The subject of his address was "The Responsibility of Being a Diabetic."

Dr. Tinsley R. Harrison, F.A.C.P., Winston-Salem, N. C., delivered the second annual J. Marion Sims Lecture on April 17, 1942, at the Medical College of the State of South Carolina in Charleston. The subject of his address was "Cardiac Dyspnea."

Dr. Orval N. Bryan, F.A.C.P., Nashville, Tenn., has been chosen President-Elect of the Tennessee State Medical Association at its annual meeting in Memphis, April 16, 1942.

At the recent meeting of the Kentucky Psychiatric Association, Dr. William K. Keller (Associate), Louisville, was installed as President.

Dr. J. Howard Holbrook, F.A.C.P., Hamilton, Ont., Canada, was recently presented with the city's Outstanding Citizenship Medal for 1941. The award was given Dr. Holbrook for his efforts over a period of thirty years to cut the death rate from tuberculosis in the city.

At the annual meeting of the North Dakota State Medical Association held in Jamestown, May 18-20, 1942, Dr. Gordon R. Kamman, F.A.C.P., St. Paul, Minn., spoke on "The Depressed Patient."

At the meeting of the Texas State Heart Association on May 11, 1942, the following officers were elected: President, Dr. Marvin L. Graves, F.A.C.P., Houston; Vice-President, Dr. P. B. Whitten, F.A.C.P., Dallas; Secretary-Treasurer, Dr. W. B. Whiting, F.A.C.P., Wichita Falls.

NEW EVANS MEMORIAL BUILDING, MASSACHUSETTS MEMORIAL HOSPITALS

On National Hospital Day, May 12, 1942, the new building of the Robert Dawson Evans Memorial in Boston was opened for inspection and occupancy. The Evans Memorial for Clinical Research and Preventive Medicine was originally dedicated on May 6, 1912, and throughout ensuing years it became necessary to expand the facilities. Accordingly, in 1940 Boston University purchased the old Robert Dawson Evans Memorial building on East Concord Street in Boston in order that they might expand their preclinical laboratories, and the Trustees of the Massachusetts Memorial Hospitals decided to construct the new Evans Memorial Building on East Newton Street immediately adjoining the Robinson and Collamore Buildings.

The new building contains nine floors and provides service for the group of Hospitals, such as the kitchens, dining rooms, admitting, bookkeeping and business offices, as well as the wards and laboratories of the Evans Memorial.

Dr. Chester S. Keefer, F.A.C.P., is the Director. The Department of Electrocardiography and Cardiology is under the supervision of Dr. James M. Faulkner, F.A.C.P. There will be laboratories for gastro-enterology, chemical laboratories for

investigation, a Department of Obstetrics, a Division of Bacteriology and Immunology, an Allergy Clinic, a Division of Pathology, et cetera.

Aside from the research activities of the various members of the Robert Dawson Evans Memorial staff, they will take an active part in the teaching of medical students of Boston University School of Medicine.

"It will be the constant purpose and objective of the Memorial to carry forward work in clinical research as set forth by the donor; that is to say, the investigation of the cause, prevention and treatment of disease." The inscription above the entrance of the original Memorial Building is "Truth above everything."

GRANTS-IN-AID AVAILABLE THROUGH THE NUTRITION FOUNDATION

The Nutrition Foundation, Inc., was organized December 21, 1941, to develop and support a comprehensive research and educational program in the science of nutrition. A part of the program has been planned to deal with nutrition in its immediate relation to public health. Another part of the program will be concerned with long-time studies of a more fundamental nature—the kind of exploratory research that should lay the foundation for better health and scientific guidance in the food industry of tomorrow.

The present war emergency makes it advisable to direct a fairly large part of the Foundation's activities into this field. The advice of Government agencies will be sought in relation to war emergency grants. Many of the members of its Scientific Advisory Committee are already on committees working with the National Research Council.

The Foundation does not plan to establish separate research laboratories; but instead will make its funds available to established institutions, such as universities with strong graduate divisions, where there are facilities for outstanding research work, and where the training of young people in the science of nutrition can be provided satisfactorily.

Application blanks for grants-in-aid may be obtained from the Executive Offices of the Foundation, Chrysler Building, New York City. Requests for grants will be submitted first to the Scientific Advisory Committee and then, if approved, to the Board of Trustees. Dr. Karl T. Compton, President of Massachusetts Institute of Technology, is the Chairman of the Board of Trustees of the Foundation.

OBITUARY

DR. I. SETH HIRSCH

Dr. I. Seth Hirsch was born December 3, 1880, in New York, N. Y., and died on March 24, 1942, at Mount Sinai Hospital, after a brief illness.

Dr. Hirsch attended the College of the City of New York from 1895 to 1898 and received his M.D. degree from the Columbia University College of Physicians and Surgeons in 1902. Between 1904 and 1914 he was Radiologist at several hospitals, including Mount Sinai, Beth Israel, Lebanon, City and Joint Diseases. Between 1910 and 1926 he was Director of the Roentgenological Department of Bellevue and four allied Hospitals—Fordham, Harlem, Gouverneur, and Neponsit Beach. From 1914 to 1917 he was Professor of Roentgenology at the New York Post Graduate Medical School, and since 1933 was Professor of Radiology at the New York University College of Medicine. For many years Dr. Hirsch was Director of the Roentgenological Department of Beth Israel Hospital and a Roentgenological Consultant to the New York State Compensation Commission.

Dr. Hirsch served with the armed forces of the United States during World War I and in 1919 was commissioned a Major in the Medical Reserve Corps of the United States Army.

At Bellevue in 1923 Dr. Hirsch conducted an experiment in the use of roentgen-ray apparatus in cancer treatment which physicians termed one of the most noteworthy up to that time. He exposed a woman cancer patient to a roentgen-ray current of 250,000 volts for a total of fifty-six hours. It was the first time that such a high voltage had ever been used for so long a period. This experiment followed a year and a half of preparation by Dr. Hirsch.

One of Dr. Hirsch's avocations was sculpture. He founded the New York Physicians Art Club, which held annual exhibitions of plastic and graphic art executed by physicians and entered much of his own sculpture.

Dr. Hirsch was a Fellow of the New York Academy of Medicine, the American Editors Association, the British Roentgen Society, the German Roentgen Society, member and a former Vice President of the Radiological Society of North America. He was a Fellow of the American Medical Association, member of the New York State and County Societies, a Fellow of the American College of Physicians since 1920.

In 1939, one-hundred and fifty friends, former students and colleagues honored Dr. Hirsch at a testimonial dinner and published a volume in his honor, entitled "Contributions to Radiology," which contained forty-five scientific articles. Dr. Hirsch also received an oil portrait of himself which had hung in the New York University College of Medicine and later was transferred to his home in New York.

Among the honors which came to Dr. Hirsch were a diploma in radiology from Cambridge University, in England, and honorary membership in Alpha Omega Alpha, honorary medical fraternity.

Dr. Hirsch practiced medicine in New York City for forty years, and was the author of "Principles and Practices of Roentgen Technique" and "Principles and Practices of Roentgen Therapy." He had written extensively on his specialty and had two books in preparation at the time of his death. He had also served as Associate Editor and Director of the Department of Technique and New Services of the American Journal of Electrology and Radiology.

Dr. Hirsch leaves a widow, two sisters, and four brothers, all of New York City.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

ANNALS OF INTERNAL MEDICINE

AUTHOR INDEX

Volume 16, January-June, 1942

- ABELS, J. C., P. E. REKERS, G. E. BINKLEY, G. T. PACK and C. P. RHOADS. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. II. Hepatic Dysfunction..... 221
- ADAMS, W. L., JR., E. L. ARMSTRONG,— L. J. TRAGERMAN and E. W. TOWNSEND. The Cruveilhier-Baumgarten Syndrome: Review of the Literature and Report of Two Additional Cases. 113
- ALLISON, B. R. The Treatment of Acute Carbon Tetrachloride Poisoning with a Report of Two Cases..... 81
- ALMY, T. P., E. TOLSTOI, — and V. TOSCANI. Treatment of Diabetes Mellitus with Protamine Insulin: Is a Persistent Glycosuria Harmful? A Metabolic Study of a Severe Case... 893
- ANDERSON, W. N. Physical Diagnosis. *Rev.*..... 582
- ARMSTRONG, E. L., W. L. ADAMS, JR., L. J. TRAGERMAN and E. W. TOWNSEND. The Cruveilhier-Baumgarten Syndrome: Review of the Literature and Report of Two Additional Cases. 113
- ARMSTRONG, J. M. History of Pioneer Medical Practice in St. Paul..... 219
- AVERBUCK, S. H. Masked Hyperthyroidism as a Cause of Heart Disease (with Report of a Case with Long Standing Auricular Fibrillation Cured by Subtotal Thyroidectomy). *Case Rep.*..... 1011
- BANOWITCH, M. M., S. H. POLAYES and R. CHARET. Periarteritis Nodosa: Report of Five Cases..... 1149
- BATSON, O. V. The Rôle of the Vertebral Veins in Metastatic Processes... 38
- BERGER, L., H. MANDELBAUM, — and M. LEDERER. Gaucher's Disease. I. A Case with Hemolytic Anemia and Marked Thrombopenia; Improvement after Removal of Spleen Weighing 6822 Grams. A. E. SOBEL and I. A. KAYE. II. Lipid Analysis of the Gaucher's Spleen..... 438
- BERKWITZ, N. J. The Treatment of Delirium Tremens with Faradic Shock Therapy; A New Approach Based upon the Psychobiological Concept.. 480
- BERNSTEIN, A., A. E. PARSONNET and —. Heart Strain: A Critical Review; The Development of a Physiologic Concept..... 1123
- BINKLEY, G. E., J. C. ABELS, P. E. REKERS, — G. T. PACK and C. P. RHOADS. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. II. Hepatic Dysfunction..... 221
- BLACKFORD, S. D., R. M. BIRD, JR. and S. W. CASSCELLS. Non-Operative Results in Ninety Patients with Abnormal Cholecystograms..... 1118
- BLANKSTEIN, S. S., N. ENZER, E. SIMONSON and —. Fatigue of Patients with Circulatory Insufficiency, Investigated by Means of the Fusion Frequency of Flicker..... 701
- BORNSTEIN, S. Heterophile Antibody Reaction Caused by Bacterial Infection..... 472
- BOWER, A. G., L. S. SIEGEL, L. ROSEVE and —. Sulfanilamide in the Treatment of Erysipelas..... 262
- BRACELAND, F. J. Mental Symptoms Following Carbon Disulphide Absorption and Intoxication..... 246
- BRANDALEONE, H., E. P. RALLI, — and H. D. FEIN. Observations on the Comparable Effects of Protamine Zinc and Regular Insulin in Diabetic Patients Followed over a Period of Years..... 750
- BRILL, N. Q. and H. SEIDEMANN. Electroencephalographic Changes during Hyperventilation in Epileptic and Non-Epileptic Disorders..... 451

- BULLOWA, J. G. M., N. H. SHACKMAN and D. STATS. Chemotherapy of Pneumonias and Immunity Reactions 57
- BUNIM, J. J. and M. ISRAEL. Acute Hemolytic Anemia Caused by Sulfathiazole. *Case Rep.*..... 333
- BURCHELL, H. B., N. M. KEITH, A. E. OSTERBERG and —. Some Effects of Potassium Salts in Man..... 879
- BURWELL, C. S. The Pathological Physiology of the Early Manifestations of Left Ventricular Failure.... 104
- CAMPBELL, E. P. Meningococcal Meningitis; Report of Fifty Cases, Forty Treated with Serum and Ten Treated with Serum and Sulfanilamide..... 694
- CARNS, M. L. Uveoparotitis. *Case Rep.*..... 1239
- CASSCELLS, S. W., S. D. BLACKFORD, R. M. BIRD, JR. and —. Non-Operative Results in Ninety Patients with Abnormal Cholecystograms.... 1118
- CECIL, R. L., W. H. KAMMERER and F. J. DEPRUME. Gold Salts in the Treatment of Rheumatoid Arthritis; A Study of 245 Cases..... 811
- CHARET, R., M. M. BANOWITCH, S. H. POLAYES and —. Periarthritis Nodosa: Report of Five Cases..... 1149
- CHASNOFF, J., L. FRIEDFELD and A. M. TUNICK. Hyperparathyroidism in a Patient with Acromegaly. *Case Rep.* 162
- CHODOFF, P., J. A. MUFSON and —. Convulsions in Paget's Disease; Electroencephalographic Observations... 762
- COCHRAN, R. M., F. L. DUNN, W. E. RAHM, JR. and —. Electroretinography. I. Cathode Ray Visualization of Lung Chest Sounds..... 521
- COHN, S., I. ROTHSTEIN and —. Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy. *Case Rep.*..... 152
- COOKE, R. A. Protein Derivatives as Factors in Allergy..... 71
- CURING, W. C. and E. H. SULTAN. Sulfonamides: Passage into Spinal Fluid and Rectal Absorption..... 708
- DAVIS, P. L. and M. S. DAVIS. Non-Icteric Leptospirosis Icterohemorrhagia (Weil's Disease) Contracted while Bathing. *Case Rep.*..... 569
- DAY, E., G. W. THORN, S. S. DORRANCE and —. Addison's Disease: Evaluation of Synthetic Desoxycorticosterone Acetate Therapy in 158 Patients. 1053
- DENMAN, H. C. Subacute Bacterial Endocarditis; An Analysis of Fifty Cases with Autopsy Findings..... 904
- DEPRUME, F. J., R. L. CECIL, W. H. KAMMERER and —. Gold Salts in the Treatment of Rheumatoid Arthritis; A Study of 245 Cases..... 811
- DOAN, C. A., B. K. WISEMAN and —. Primary Splenic Neutropenia; A Newly Recognized Syndrome, Closely Related to Congenital Hemolytic Icterus and Essential Thrombocytopenic Purpura..... 1097
- DORRANCE, S. S., G. W. THORN, — and E. DAY. Addison's Disease: Evaluation of Synthetic Desoxycorticosterone Acetate Therapy in 158 Patients. 1053
- DRAPER, G. The Emotional Component of the Ulcer Susceptible Constitution..... 633
- DUNBAR, H. F. Emotions and Bodily Changes: A Survey of Literature on Psychosomatic Interrelationships, 1910-1933. *Rev.*..... 180
- DUNCAN, G. G., Editor. Diseases of Metabolism. *Rev.*..... 1256
- DUNN, F. L., W. E. RAHM, JR. and R. M. COCHRAN. Electroretinography. I. Cathode Ray Visualization of Lung Chest Sounds..... 521
- DUTTON, W. F. Headache and Head Pains. *Rev.*..... 371
- ELSON, K. A. and F. J. INGELFINGER. Eosinophilia and Pneumonitis in Chronic Brucellosis; A Report of Two Cases..... 995
- ENZER, N., E. SIMONSON and S. S. BLANKSTEIN. Fatigue of Patients with Circulatory Insufficiency, Investigated by Means of the Fusion Frequency of Flicker..... 701
- FEIN, H. D., E. P. RALLI, H. BRANDALEONE and —. Observations on the Comparable Effects of Protamine Zinc and Regular Insulin in Diabetic

- Patients Followed over a Period of Years..... 750
- FELS, S. S., H. SHAY, J. GERSHON-COHEN and —. A Theory Explaining the Local Mechanism for Gastric Motor and Secretory Control and the Alteration of These Functions in Uncomplicated Duodenal Ulcer..... 772
- FINLAND, M., E. STRAUSS and O. L. PETERSON. Antibody Response of Patients with Pneumococcic Pneumonia Treated with Sulfadiazine and Sulfathiazole..... 1
- FINLAND, M., E. STRAUSS and —. Further Studies on Recurrences in Pneumococcic Pneumonia with Special Reference to the Effect of Specific Treatment..... 17
- FOSTER, R. C. Gonococcus Bacteremia with Joint and Skin Manifestations. *Case Rep.*..... 1018
- FREYBERG, R. H., C. J. SMYTH and —. A Study of the Hereditary Nature of Gout; A Report of Two Families.... 46
- FRIEDFELD, L., J. CHASNOFF, — and A. M. TUNICK. Hyperparathyroidism in a Patient with Acromegaly. *Case Rep.*..... 162
- GALLI-MAININI, C. Exophthalmometric Measurements in Patients with Thyroid Diseases with Some Discussion of Their Significance..... 415
- GERSHON-COHEN, J., H. SHAY, — and S. S. FELS. A Theory Explaining the Local Mechanism for Gastric Motor and Secretory Control and the Alteration of These Functions in Uncomplicated Duodenal Ulcer..... 772
- GIBB, W. T., JR. A Theory Concerning the Manner in Which the Stomach Empties Itself..... 94
- GOLD, H. and B. HAMPIL. Equine Encephalomyelitis in a Laboratory Technician with Recovery. *Case Rep.*.... 556
- GREENE, B. A. Recent Advances in the Care of the Comatose Patient... 727
- GROSS, H. and M. SANDBERG. The Concentration of Creatine in Heart, Diaphragm, and Skeletal Muscle in Uremia..... 737
- GUSTAFSON, E. G., H. F. WECHSLER and —. Brucella Endocarditis of Congenital Bicuspid Aortic Valve. *Case Rep.*..... 1228
- HADDEN, S. B. Treatment of the Neuroses by Class Technic..... 33
- HAMPIL, B., H. GOLD and —. Equine Encephalomyelitis in a Laboratory Technician with Recovery. *Case Rep.* 556
- HANES, E. L. The Minds and Nerves of Soldiers. *Rev.*..... 180
- HARBIN, W., JR. and T. S. HARBIN. Uveoparotitis: A Report of Two Cases. *Case Rep.*..... 360
- HARRIS, H. J. Brucellosis (Undulant Fever); Clinical and Subclinical. *Rev.*..... 1027
- HEILIG, R. and N. L. KANTIENGAR. Liver Function in Menstruation.... 538
- HERTZLER, A. E. Diseases of the Thyroid Gland. *Rev.*..... 179
- HESS, J. H. and E. C. LUNDEEN. The Premature Infant; Its Medical and Nursing Care. *Rev.*..... 179
- HILL, J. M., E. E. MUIRHEAD and —. The Advantages and Clinical Uses of Desiccated Plasma Prepared by the Adtevac Process..... 286
- INGELFINGER, F. J., K. A. ELSOM and —. Eosinophilia and Pneumonitis in Chronic Brucellosis; A Report of Two Cases..... 995
- ISRAEL, M., J. J. BUNIM and —. Acute Hemolytic Anemia Caused by Sulfathiazole. *Case Rep.*..... 333
- JOACHIM, H. Practical Bedside Diagnosis and Treatment. *Rev.*..... 179
- JONES, G. M., JR. Periarthritis Nodosa; with Case Reports..... 920
- JULIANELLE, L. A. Observations on the Specific Treatment (Type A Antiserum) of Staphylococcal Sepsis; Second Report..... 303
- JUSTER, I. R. The Relationship of Upper Respiratory Infections to Rheumatic Activity in Chronic Rheumatic Heart Disease..... 1137
- KAMMERER, W. H., R. L. CECIL, — and F. J. DEPRUME. Gold Salts in the Treatment of Rheumatoid Arthritis; A Study of 245 Cases..... 811
- KANTIENGAR, N. L., R. HEILIG and —. Liver Function in Menstruation.... 538

- KATZ, L. N., M. SOKOLOW, H. B. WEINBERG, J. L. PLAUT and —. Digitalis in the Prevention of Recurrent Cardiac Failure in Patients with Sinus Rhythm..... 427
- KAYE, I. A., A. E. SOBEL and —. Gaucher's Disease. II. Lipid Analysis of the Gaucher's Spleen. I. A Case with Hemolytic Anemia and Marked Thrombopenia: Improvement after Removal of Spleen Weighing 6822 Grams. H. MANDELBAUM, L. BERGER and M. LEDERER. —... 438
- KEEFER, C. S. and C. H. RAMMELKAMP. *H. Influenzae* Bacteremia; Report of Two Cases Recovering Following Sulfathiazole and Sulfapyridine. *Case Rep.*..... 1221
- KEEFER, C. S., C. H. RAMMELKAMP and —. Sulfadiazine; A Study of Its Effect on Hemolytic Streptococci.... 659
- KEIL, H. The Manifestations in the Skin and Mucous Membranes in Dermatomyositis, with Special Reference to the Differential Diagnosis from Systemic Lupus Erythematosus. 828
- KEITH, N. M., A. E. OSTERBERG and H. B. BURCHELL. Some Effects of Potassium Salts in Man..... 879
- KEYS, T. E., F. A. WILLIUS and —. Cardiac Classics. *Rev.*..... 583
- KING, J. T. Anticipation and Diagnosis of Neurocirculatory Asthenia..... 941
- KING, J. T. Certain Infections in the Background of Patients with Coronary Occlusion..... 462
- KWEDAR, A. T. The Waterhouse-Friderichsen Syndrome: Report of a Case in an Adult. *Case Rep.*..... 787
- LEAMAN, W. G., JR. Management of the Cardiac Patient. *Rev.*..... 581
- LEDERER, M., H. MANDELBAUM, L. BERGER and —. Gaucher's Disease. I. A Case with Hemolytic Anemia and Marked Thrombopenia; Improvement after Removal of Spleen Weighing 6822 Grams. A. E. SOBEL and I. A. KAYE. II. Lipid Analysis of the Gaucher's Spleen..... 438
- LILIENFELD, A., A. D. TANNEY and —. The Cardiovascular Aspects of Carotid Sinus Hypersensitivity with Special Reference to Some Cardiac Arrhythmias..... 676
- LUNDEEN, E. C., J. H. HESS and —. The Premature Infant; Its Medical and Nursing Care. *Rev.*..... 179
- MAGNUSON, H. J. and B. O. RAULSTON. The Iron Content of the Skin in Hemochromatosis..... 687
- MANCHESTER, R. C. The Clinical Manifestations and Diagnosis of Chronic Brucellosis..... 950
- MANDELBAUM, H., L. BERGER and M. LEDERER. Gaucher's Disease. I. A Case with Hemolytic Anemia and Marked Thrombopenia; Improvement after Removal of Spleen Weighing 6822 Grams. A. E. SOBEL and I. A. KAYE. II. Lipid Analysis of the Gaucher's Spleen..... 438
- MARTIN, W. B., L. WAITZKIN, R. H. SMITH and —. Sulfonamides and Heparin in the Treatment of Subacute Bacterial Endocarditis. *Case Rep.*..... 356
- MCGUIGAN, H. A. Applied Pharmacology. *Rev.*..... 370
- MEAKINS, J. C. William Withering: His Contribution to Medicine..... 327
- MENDELL, T. H., D. R. MERANZE and T. MERANZE. The Clinical Value of Sternal Bone Marrow Puncture..... 1180
- MERVES, L., R. B. NYE, C. W. SEMISCH and —. Chronic Meningococcemia Complicated by Acute Endocarditis. *Case Rep.*..... 1245
- MILLER, J. A. Whither?..... 1003
- MUFSON, J. A. and P. CHODOFF. Convulsions in Paget's Disease; Electroencephalographic Observations..... 762
- MUHL, A. M. The A B C of Criminology. *Rev.*..... 582
- MUIRHEAD, E. E. and J. M. HILL. The Advantages and Clinical Uses of Desiccated Plasma Prepared by the Adtevac Process..... 286
- MULVEY, B. E. and L. A. RIELY. Status Dysraphicus and Syringomyelia..... 966
- NYE, R. B., C. W. SEMISCH and L. MERVES. Chronic Meningococcemia Complicated by Acute Endocarditis. *Case Rep.*..... 1245

- NYGAARD, K. K. Hemorrhagic Dis-
 cases: Photo-Electric Study of Blood
 Coagulability. *Rev.*..... 371
- O'NEILL, D. B., C. WEYL, S. R. WAR-
 REN, JR. and —. Radiologic Physics.
Rev...... 370
- OSTERBERG, A. E., N. M. KEITH, — and
 H. B. BURCHELL. Some Effects of
 Potassium Salts in Man..... 879
- PACK, G. T., J. C. ABELS, P. E. REKERS,
 G. E. BINKLEY, — and C. P. RHOADS.
 Metabolic Studies in Patients with
 Cancer of the Gastrointestinal Tract.
 II. Hepatic Dysfunction..... 221
- PARDO-CASTELLO, V. Diseases of the
 Nails. *Rev.*..... 1027
- PARKS, H. An Instance of Coronary
 Embolism in Subacute Bacterial En-
 docarditis. *Case Rep.*..... 339
- PARSONNET, A. E. and A. BERNSTEIN.
 Heart Strain: A Critical Review; The
 Development of a Physiologic Con-
 cept..... 1123
- PATTON, E. W., J. B. YOUMANS and —.
 Nutritional Deficiencies; Diagnosis
 and Treatment. *Rev.*..... 1256
- PAULSON, M. and C. I. WYLER. Mul-
 tiple Tests of Hepatic Function in
 Gastroenteric Malignancy: The Value
 of Bromsulphalein, Hippuric Acid and
 the van den Bergh Reaction in De-
 tecting Hepatic Metastasis, with an
 Evaluation of Normality of the Hip-
 puric Acid Test..... 872
- PETERS, H. R. Anuria Following Hem-
 olytic Reaction to Blood Transfusion:
 Recovery Following Splanchnic Block.
Case Rep...... 547
- PETERSON, O. L., M. FINLAND, E.
 STRAUSS and —. Antibody Response
 of Patients with Pneumococcic Pneu-
 monia Treated with Sulfadiazine and
 Sulfathiazole..... 1
- PLAUT, J. L., M. SOKOLOW, H. B.
 WEINBERG, — and L. N. KATZ.
 Digitalis in the Prevention of Recur-
 rent Cardiac Failure in Patients with
 Sinus Rhythm..... 427
- PLUMMER, N., C. WHEELER and —.
 Sulfadiazine and Sodium Sulfadia-
 zine: A Comparison of Certain of
 Their Clinical and Pharmacologic
 Values..... 269
- POLAYES, S. H., M. M. BANOWITCH, —
 and R. CHARET. Periarthritis No-
 dosa: Report of Five Cases..... 1149
- RAHM, W. E., JR., F. L. DUNN, — and
 R. M. COCHRAN. Electrostethog-
 raphy. I. Cathode Ray Visualiza-
 tion of Lung Chest Sounds..... 521
- RAISBECK, M. J., S. A. THOMPSON and
 —. Cardio-Pericardiopexy; The Sur-
 gical Treatment of Coronary Arterial
 Disease by the Establishment of Ad-
 hesive Pericarditis..... 495
- RAKOV, H. L. Ventricular Fibrillation
 in Acute Coronary Artery Thrombo-
 sis during the Intravenous Adminis-
 tration of Quinidine Sulphate; Report
 of a Fatal Case. *Case Rep.*..... 571
- RALLI, E. P., H. BRANDALEONE and H.
 D. FEIN. Observations on the Com-
 parable Effects of Protamine Zinc and
 Regular Insulin in Diabetic Patients
 Followed over a Period of Years.... 750
- RAMMELKAMP, C. H. and C. S. KEEFER.
 Sulfadiazine; A Study of Its Effect on
 Hemolytic Streptococci..... 659
- RAMMELKAMP, C. H., C. S. KEEFER and
 —. *H. Influenzae* Bacteremia: Re-
 port of Two Cases Recovering Fol-
 lowing Sulfathiazole and Sulfapyri-
 dine. *Case Rep.*..... 1221
- RANTZ, L. A. Streptococcal Meningitis:
 Four Cases Treated with Sulfon-
 amides in Which the Etiological
 Agent Was an Unusual Strepto-
 coccus..... 716
- RASMUSSEN, A. T. The Principal Ner-
 vous Pathways. *Rev.*..... 371
- RAULSTON, B. O., H. J. MAGNUSON and
 —. The Iron Content of the Skin in
 Hemochromatosis..... 687
- REDNICK, M. S. A Pathological Study
 of the Significance of the Systolic
 Murmur..... 1197
- REINER, M. Manual of Clinical Chem-
 istry. *Rev.*..... 796
- REKERS, P. E., J. C. ABELS, — G. E.
 BINKLEY, G. T. PACK and C. P.
 RHOADS. Metabolic Studies in Pa-
 tients with Cancer of the Gastro-
 intestinal Tract. II. Hepatic Dys-
 function..... 221

- RHOADS, C. P., J. C. ABELS, P. E. REKERS, G. E. BINKLEY, G. T. PACK and —. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. II. Hepatic Dysfunction..... 221
- RIELY, L. A., B. E. MULVEY and —. Status Dysraphicus and Syringomyelia..... 966
- ROSOVE, L., L. S. SIEGEL, — and A. G. BOWER. Sulfanilamide in the Treatment of Erysipelas..... 262
- ROTHSTEIN, I. and S. COHN. Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy. *Case Rep.*..... 152
- SANDBERG, M., H. GROSS and —. The Concentration of Creatine in Heart, Diaphragm, and Skeletal Muscle in Uremia..... 737
- SCHERLIS, S. Response to Sulfapyridine in 241 Cases of Pneumonia, with Especial Reference to Lack of Prompt Response in Some Cases..... 666
- SEIDEMANN, H., N. Q. BRILL and —. Electroencephalographic Changes during Hyperventilation in Epileptic and Non-Epileptic Disorders..... 451
- SEMISCH, C. W., R. B. NYE, — and L. MERVES. Chronic Meningococcemia Complicated by Acute Endocarditis. *Case Rep.*..... 1245
- SHACKMAN, N. H., J. G. M. BULLOWA, — and D. STATS. Chemotherapy of Pneumonias and Immunity Reactions 57
- SHAY, H., J. GERSHON-COHEN and S. S. FELS. A Theory Explaining the Local Mechanism for Gastric Motor and Secretory Control and the Alteration of These Functions in Uncomplicated Duodenal Ulcer..... 772
- SHERWOOD, N. P. Immunology. *Rev.* 1256
- SHUMAN, H., D. SNIVELY, — and W. D. SNIVELY. Spontaneous Hemopneumothorax. *Case Rep.*..... 349
- SIEGEL, L. S., L. ROSOVE and A. G. BOWER. Sulfanilamide in the Treatment of Erysipelas..... 262
- SILVERMAN, E. G., B. L. ZOHMAN and —. Infectious Mononucleosis and Encephalomyelitis. *Case Rep.*..... 1233
- SIMONSON, E., N. ENZER, — and S. S. BLANKSTEIN. Fatigue of Patients with Circulatory Insufficiency, Investigated by Means of the Fusion Frequency of Flicker..... 701
- SLOCUMB, C. H. Vitamin D in the Treatment of Infectious Arthritis.... 241
- SMITH, R. H., L. WAITZKIN, — and W. B. MARTIN. Sulfonamides and Heparin in the Treatment of Subacute Bacterial Endocarditis. *Case Rep.*... 356
- SMITHWICK, R., J. WHITE and —. The Autonomic Nervous System. *Rev.*... 796
- SMYTH, C. J. and R. H. FREYBERG. A Study of the Hereditary Nature of Gout; A Report of Two Families.... 46
- SNAPPER, I. Chinese Lessons to Western Medicine. *Rev.*..... 1027
- SNIVELY, D., H. SHUMAN and W. D. SNIVELY. Spontaneous Hemopneumothorax. *Case Rep.*..... 349
- SNOW, W. Clinical Roentgenology of Pregnancy. *Rev.*..... 796
- SOBEL, A. E. and I. A. KAYE. Gaucher's Disease. II. Lipid Analysis of the Gaucher's Spleen. I. A Case with Hemolytic Anemia and Marked Thrombopenia; Improvement after Removal of Spleen Weighing 6822 Grams. H. MANDELBAUM, L. BERGER and M. LEDERER. —..... 438
- SOKOLOW, M., H. B. WEINBERG, J. L. PLAUT and L. N. KATZ. Digitalis in the Prevention of Recurrent Cardiac Failure in Patients with Sinus Rhythm 427
- STATS, D., J. G. M. BULLOWA, N. H. SHACKMAN and —. Chemotherapy of Pneumonias and Immunity Reactions..... 57
- STRAUSS, E. and M. FINLAND. Further Studies on Recurrences in Pneumococcic Pneumonia with Special Reference to the Effect of Specific Treatment..... 17
- STRAUSS, E., M. FINLAND — and O. L. PETERSON. Antibody Response of Patients with Pneumococcic Pneumonia Treated with Sulfadiazine and Sulfathiazole..... 1
- SULTAN, E. H., W. C. CUTTING and —. Sulfonamides: Passage into Spinal Fluid and Rectal Absorption..... 703

- TANNEY, A. D. and A. LILIENFELD.
The Cardiovascular Aspects of Carotid Sinus Hypersensitivity with Special Reference to Some Cardiac Arrhythmias..... 676
- THOMPSON, R. M. Neuroblastoma (Sympathoblastoma or Neurocytoma) of the Suprarenal Medulla; Report of Three Cases. *Case Rep.*..... 1206
- THOMPSON, S. A. and M. J. RAISBECK.
Cardio-Pericardiopexy; The Surgical Treatment of Coronary Arterial Disease by the Establishment of Adhesive Pericarditis..... 495
- THORN, G. W., S. S. DORRANCE and E. DAY.
Addison's Disease: Evaluation of Synthetic Desoxycorticosterone Acetate Therapy in 158 Patients.... 1053
- TOLSTOI, E., T. P. ALMY and V. TOSCANI.
Treatment of Diabetes Mellitus with Protamine Insulin: Is a Persistent Glycosuria Harmful? A Metabolic Study of a Severe Case... 893
- TOP, F. H. and collaborators. *Handbook of Communicable Diseases. Rev.*..... 1257
- TRAGERMAN, L. J., E. L. ARMSTRONG, W. L. ADAMS, JR.—and E. W. TOWNSEND.
The Cruveilhier-Baumgarten Syndrome: Review of the Literature and Report of Two Additional Cases..... 113
- TUNICK, A. M., J. CHASNOFF, L. FRIEDFELD and —.
Hyperparathyroidism in a Patient with Acromegaly. *Case Rep.*..... 162
- WAITZKIN, L., R. H. SMITH and W. B. MARTIN.
Sulfonamides and Heparin in the Treatment of Subacute Bacterial Endocarditis. *Case Rep.*..... 356
- WARREN, S. R., JR., C. WEYL, — and D. B. O'NEILL.
Radiologic Physics. Rev...... 370
- WECHSLER, H. F. and E. G. GUSTAFSON.
Brucella Endocarditis of Congenital Bicuspid Aortic Valve. *Case Rep.*... 1228
- WEINBERG, H. B., M. SOKOLOW, — J. L. PLAUT and L. N. KATZ.
Digitalis in the Prevention of Recurrent Cardiac Failure in Patients with Sinus Rhythm 427
- WEYL, C., S. R. WARREN, JR. and D. B. O'NEILL.
Radiologic Physics. Rev. 370
- WHEELER, C. and N. PLUMMER.
Sulfadiazine and Sodium Sulfadiazine: A Comparison of Certain of Their Clinical and Pharmacologic Values..... 269
- WHITE, J. and R. SMITHWICK.
The Autonomic Nervous System. *Rev.*... 796
- WILLIS, W. H.
Thrombocytopenic Purpura and Carcinoma of Stomach; Report of a Case with Purpura Appearing after Subtotal Gastrectomy. *Case Rep.*..... 782
- WILLIUS, F. A. and T. E. KEYS.
Cardiac Classics. Rev...... 583
- WISEMAN, B. K. and C. A. DOAN.
Primary Splenic Neutropenia; A Newly Recognized Syndrome, Closely Related to Congenital Hemolytic Icterus and Essential Thrombocytopenic Purpura..... 1097
- WYLER, C. I., M. PAULSON and —.
Multiple Tests of Hepatic Function in Gastroenteric Malignancy: The Value of Bromsulphalein, Hippuric Acid and the van den Bergh Reaction in Detecting Hepatic Metastasis, with an Evaluation of Normality of the Hippuric Acid Test..... 872
- YOUSMANS, J. B. and E. W. PATTON.
Nutritional Deficiencies; Diagnosis and Treatment. *Rev.*..... 1256
- ZOHMAN, B. L. and E. G. SILVERMAN.
Infectious Mononucleosis and Encephalomyelitis. *Case Rep.*..... 1233

ANNALS OF INTERNAL MEDICINE

SUBJECT INDEX

Volume 16, January-June, 1942

- A** CROMEGALY, Hyperparathyroidism in a Patient with—. J. CHASNOFF, L. FRIEDFELD and A. M. TUNICK. *Case Rep.*..... 162
- Addison's Disease: Evaluation of Synthetic Desoxycorticosterone Acetate Therapy in 158 Patients. G. W. THORN, S. S. DORRANCE and E. DAY. 1053
- Adtevac Process, The Advantages and Clinical Uses of Desiccated Plasma Prepared by the—. E. E. MUIRHEAD and J. M. HILL..... 286
- Allergy, Protein Derivatives as Factors in—. R. A. COOKE..... 71
- Antibody Response of Patients with Pneumococcic Pneumonia Treated with Sulfadiazine and Sulfathiazole. M. FINLAND, E. STRAUSS and O. L. PETERSON..... 1
- Anuria Following Hemolytic Reaction to Blood Transfusion; Recovery Following Splanchnic Block. H. R. PETERS. *Case Rep.*..... 547
- Arthritis, Gold Salts in the Treatment of Rheumatoid—; A Study of 245 Cases. R. L. CECIL, W. H. KAMMERER and F. J. DEPRUME..... 811
- Arthritis, Vitamin D in the Treatment of Infectious—. C. H. SLOCUMB.... 241
- Autonomic Nervous System, The—. J. WHITE and R. SMITHWICK. *Rev.* 796
- B**ACTEREMIA, Gonococcus—with Joint and Skin Manifestations; Case Report. R. C. FOSTER. *Case Rep.*..... 1018
- Bacterial Infection, Heterophile Antibody Reaction Caused by—. S. BORNSTEIN..... 472
- Brucella Endocarditis of Congenital Bicuspid Aortic Valve. H. F. WECHSLER and E. G. GUSTAFSON. *Case Rep.*..... 1228
- Brucellosis, Eosinophilia and Pneumonitis in Chronic—; A Report of Two Cases. K. A. ELSOM and F. J. INGELFINGER..... 995
- Brucellosis, The Clinical Manifestations and Diagnosis of Chronic—. R. C. MANCHESTER..... 950
- Brucellosis (Undulant Fever); Clinical and Subclinical. H. J. HARRIS. *Rev.* 1027
- C**ANCER of the Gastrointestinal Tract, Metabolic Studies in Patients with—. II. Hepatic Dysfunction. J. C. ABELS, P. E. REKERS, G. E. BINKLEY, G. T. PACK and C. P. RHOADS..... 221
- Carbon Disulphide Absorption and Intoxication, Mental Symptoms Following—. F. J. BRACELAND..... 246
- Carbon Tetrachloride Poisoning, The Treatment of Acute—with a Report of Two Cases. B. R. ALLISON..... 81
- Carcinoma of Stomach, Thrombocytopenic Purpura and—; Report of a Case with Purpura Appearing after Subtotal Gastrectomy. W. H. WILKIS. *Case Rep.*..... 782
- Cardiac Classics. F. A. WILLIUS and T. E. KEYS. *Rev.*..... 583
- Cardiac Failure, Digitalis in the Prevention of Recurrent—in Patients with Sinus Rhythm. M. SOKOLOW, H. B. WEINBERG, J. L. PLAUT and L. N. KATZ..... 427
- Cardiac Patient, Management of the—. W. G. LEAMAN, JR. *Rev.*..... 581
- Cardio-Pericardiopexy; The Surgical Treatment of Coronary Arterial Disease by the Establishment of Adhesive Pericarditis. S. A. THOMPSON and M. J. RAISBECK..... 495
- Cardiovascular Aspects of Carotid Sinus Hypersensitivity with Special Reference to Some Cardiac Arrhythmias, The—. A. D. TANNEY and A. LILIENTHAL..... 676

- Charaka Club, The Proceedings of the
—, *Rev.*..... 797
- Chemistry, Manual of Clinical—, M.
REINER. *Rev.*..... 796
- Chemotherapy of Pneumonias and Im-
munity Reactions. J. G. M. BUL-
LOWA, N. H. SHACKMAN and D. STATS 57
- Chinese Lessons to Western Medicine.
I. SNAPPER. *Rev.*..... 1027
- Cholecystograms, Non-Operative Re-
sults in Ninety Patients with Ab-
normal—, S. D. BLACKFORD, R. M.
BIRD, JR. and S. W. CASSCELLS.... 1118
- Choriomeningitis, Lymphocytic—as a
Systemic Disease. *Edit.*..... 1023
- Circulatory Insufficiency, Fatigue of
Patients with—, Investigated by
Means of the Fusion Frequency of
Flicker. N. ENZER, E. SIMONSON
and S. S. BLANKSTEIN..... 701
- Comatose Patient, Recent Advances in
the Care of the—. B. A. GREENE.. 727
- Communicable Diseases, Handbook of
—, F. H. TOP. *Rev.*..... 1257
- Convulsions in Paget's Disease: Electro-
encephalographic Observations. J.
A. MUFSON and PAUL CHODOFF..... 762
- Coronary Artery Thrombosis, Ventric-
ular Fibrillation in Acute—during the
Intravenous Administration of Quini-
dine Sulphate; Report of a Fatal
Case. H. L. RAKOV. *Case Rep.*... 571
- Coronary Embolism in Subacute Bac-
terial Endocarditis, An Instance of—.
H. PARKS. *Case Rep.*..... 339
- Coronary Occlusion, Certain Infections
in the Background of Patients with—.
J. T. KING..... 462
- Creatine in Heart, Diaphragm, and
Skeletal Muscle in Uremia, The Con-
centration of—. H. GROSS and M.
SANDBERG..... 737
- Criminology, The A B C of—. A. M.
MUHL. *Rev.*..... 582
- Crush Syndrome. *Edit.*..... 792
- Cruveilhier-Baumgarten Syndrome, The
—: Review of the Literature and Re-
port of Two Additional Cases. E. L.
ARMSTRONG, W. L. ADAMS, JR., L. J.
TRAGERMAN and E. W. TOWNSEND.. 113
- upon the Psychobiological Concept.
N. J. BERKWITZ..... 480
- Dermatomyositis, The Manifestations
in the Skin and Mucous Membranes
in—, with Special Reference to the
Differential Diagnosis from Systemic
Lupus Erythematosus. H. KEIL... 828
- Desoxycorticosterone Acetate Therapy,
Evaluation of Synthetic—in 158 Pa-
tients. Addison's Disease:—. G. W.
THORN, S. S. DORRANCE and E. DAY. 1053
- Diabetes Mellitus, Treatment of—with
Protamine Insulin: Is a Persistent
Glycosuria Harmful? A Metabolic
Study of a Severe Case. E. TOLSTOI,
T. P. ALMY and V. TOSCANI..... 893
- Diabetic Patients Followed over a Pe-
riod of Years, Observations on the
Comparable Effects of Protamine Zinc
and Regular Insulin in—. E. P.
RALLI, H. BRANDALEONE and H. D.
FEIN..... 750
- Diagnosis and Treatment, Practical
Bedside—. H. JOACHIM. *Rev.*..... 179
- Diagnosis, Physical—. W. N. ANDER-
SON. *Rev.*..... 582
- Digitalis in the Prevention of Recurrent
Cardiac Failure in Patients with Sinus
Rhythm. M. SOKOLOW, H. B. WEIN-
BERG, J. L. PLAUT and L. N. KATZ.. 427
- Duodenal Ulcer, A Theory Explaining
the Local Mechanism for Gastric
Motor and Secretory Control and the
Alteration of These Functions in Un-
complicated—. H. SHAY, J. GER-
SHON-COHEN and S. S. FELS..... 772
- E**LECTROENCEPHALOGRAPHIC
Changes during Hyperventilation
in Epileptic and Non-Epileptic Dis-
orders. N. Q. BRILL and H. SEIDE-
MANN..... 451
- Electrostethography. I. Cathode Ray
Visualization of Lung Chest Sounds.
F. L. DUNN, W. E. RAHM, JR., and
R. M. COCHRAN..... 521
- Emotions and Bodily Changes: A Sur-
vey of Literature on Psychosomatic
Interrelationships, 1910-1933. H. F.
DUNBAR. *Rev.*..... 180
- Encephalomyelitis, Infectious Mono-
nucleosis and—. B. L. ZOHMAN and
E. G. SILVERMAN. *Case Rep.*..... 1233
- D**ELIRIUM Tremens, The Treat-
ment of—with Faradic Shock
Therapy; A New Approach Based

- Endocarditis, An Instance of Coronary Embolism in Subacute Bacterial—. H. PARKS. *Case Rep.*..... 339
- Endocarditis, Chronic Meningococcemia Complicated by Acute—. R. B. NYE, C. W. SEMISCH and L. MERVES. *Case Rep.*..... 1245
- Endocarditis, Subacute Bacterial—; An Analysis of Fifty Cases with Autopsy Findings. H. C. DENMAN..... 904
- Endocarditis, Sulfonamides and Heparin in the Treatment of Subacute Bacterial—. L. WAITZKIN, R. H. SMITH and W. B. MARTIN. *Case Rep.*..... 356
- Eosinophilia and Pneumonitis in Chronic Brucellosis; A Report of Two Cases. K. A. ELSOM and F. J. INGELFINGER. 995
- Epileptic and Non-Epileptic Disorders, Electroencephalographic Changes during Hyperventilation in—. N. Q. BRILL and H. SEIDEMANN..... 451
- Equine Encephalomyelitis in a Laboratory Technician with Recovery. H. GOLD and B. HAMPIL. *Case Rep.*.... 556
- Erysipelas, Sulfanilamide in the Treatment of—. L. S. SIEGEL, L. ROSOVE and A. G. BOWER..... 262
- Exophthalmometric Measurements in Patients with Thyroid Diseases with Some Discussion of Their Significance. C. GALLI-MAININI..... 415
- F**ARADIC Shock Therapy, The Treatment of Delirium Tremens with—; A New Approach Based upon the Psychobiological Concept. N. J. BERKWITZ..... 480
- Fatigue of Patients with Circulatory Insufficiency, Investigated by Means of the Fusion Frequency of Flicker. N. ENZER, E. SIMONSON and S. S. BLANKSTEIN..... 701
- G**ASTRIC Motor and Secretory Control, A Theory Explaining the Local Mechanism for—and the Alteration of These Functions in Uncomplicated Duodenal Ulcer. H. SHAY, J. GERSHON-COHEN and S. S. FELS. . 772
- Gastrointestinal Tract, Metabolic Studies in Patients with Cancer of the —. H. Hepatic Dysfunction. J. C. ABELS, P. E. REKERS, G. E. BINKLEY, G. T. PACK and C. P. RHODES . . . 221
- Gaucher's Disease. I. A Case with Hemolytic Anemia and Marked Thrombopenia: Improvement after Removal of Spleen Weighing 6822 Grams. H. MANDELBAUM, L. BERGER and M. LEDERER. II. Lipid Analysis of the Gaucher's Spleen. A. E. SOBEL and I. A. KAYE..... 438
- Gold Salts in the Treatment of Rheumatoid Arthritis; A Study of 245 Cases. R. L. CECIL, W. H. KAMMERER and F. J. DEPRUME..... 811
- Gonococcus Bacteremia with Joint and Skin Manifestations; Case Report. R. C. FOSTER. *Case Rep.*..... 1018
- Gout, A Study of the Hereditary Nature of—; A Report of Two Families. C. J. SMYTH and R. H. FREYBERG... 46
- H**EADACHE and Head Pains. W. F. DUTTON. *Rev.*..... 371
- Heart Disease, Masked Hyperthyroidism as a Cause of—(with Report of a Case with Long Standing Auricular Fibrillation Cured by Subtotal Thyroidectomy). S. H. AVERBUCK. *Case Rep.*..... 1011
- Heart Strain: A Critical Review; The Development of a Physiologic Concept. A. E. PARSONNET and A. BERNSTEIN..... 1123
- Hemochromatosis, The Iron Content of the Skin in—. H. J. MAGNUSON and B. O. RAULSTON..... 687
- Hemolytic Anemia, Acute—, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy; Case Report. I. ROTHSTEIN and S. COHN. *Case Rep.* 152
- Hemolytic Anemia, Acute—Caused by Sulfathiazole. J. J. BUNIM and M. ISRAEL. *Case Rep.*..... 333
- Hemolytic Reaction to Blood Transfusion, Anuria Following—; Recovery Following Splanchnic Block. H. R. PETERS. *Case Rep.*..... 547
- Hemolytic Streptococci, A Study of Its Effect on—. Sulfadiazine; —. C. H. RAMMELKAMP and C. S. KEEFER... 659
- Hemopneumothorax, Spontaneous—; Report of a Case. D. SNIVELY, H. SHUMAN and W. D. SNIVELY. *Case Rep.*..... 349

- Hemorrhagic Diseases: Photo-Electric Study of Blood Coagulability. K. K. NYGAARD. *Rev.*..... 371
- Heparin, Sulfonamides and—in the Treatment of Subacute Bacterial Endocarditis. L. WAITZKIN, R. H. SMITH and W. B. MARTIN. *Case Rep.* 356
- Hepatic Dysfunction. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. II.—J. C. ABELS, P. E. REKERS, G. E. BINKLEY, G. T. PACK and C. P. RHOADS..... 221
- Hepatic Function in Gastroenteric Maligancy, Multiple Tests of—: The Value of Bromsulphalein, Hippuric Acid and the van den Bergh Reaction in Detecting Hepatic Metastasis, with an Evaluation of Normality of the Hippuric Acid Test. M. PAULSON and C. I. WYLER..... 872
- Heterophile Antibody Reaction Caused by Bacterial Infection. S. BORNSTEIN..... 472
- H. Influenzae* Bacteremia: Report of Two Cases Recovering Following Sulfathiazole and Sulfapyridine. C. S. KEEFER and C. H. RAMMELKAMP. *Case Rep.*..... 1221
- History of Pioneer Medical Practice in St. Paul. J. M. ARMSTRONG..... 219
- Hypercalcemia and Renal Injury. *Edit.* 176
- Hyperparathyroidism in a Patient with Acromegaly. J. CHASNOFF, L. FRIEDFELD and A. M. TUNICK. *Case Rep.* 162
- Hyperthyroidism, Masked—as a Cause of Heart Disease (with Report of a Case with Long Standing Auricular Fibrillation Cured by Subtotal Thyroidectomy). S. H. AVERBUCK. *Case Rep.*..... 1011

- I**MMUNOLOGY. N. P. SHERWOOD. *Rev.*..... 1256
- Infectious Mononucleosis and Encephalomyelitis. B. L. ZOHMAN and E. G. SILVERMAN. *Case Rep.*..... 1233
- Insulin, Observations on the Comparable Effects of Protamine Zinc and Regular—in Diabetic Patients Followed over a Period of Years. E. P. RALLI, H. BRANDALEONE and H. D. FEIN..... 750

- Insulin, Treatment of Diabetes Mellitus with Protamine—: Is a Persistent Glycosuria Harmful? A Metabolic Study of a Severe Case. E. TOLSTOI, T. P. ALMY and V. TOSCANI..... 893
- Iron Content of the Skin in Hemochromatosis, The—. H. J. MAGNUSON and B. O. RAULSTON..... 687

- L**EPTOSPIROSIS Icterohemorrhagia, Non-Icteric—(Weil's Disease) Contracted while Bathing. P. L. DAVIS and M. S. DAVIS. *Case Rep.* 569
- Liver Function in Menstruation. R. HEILIG and N. L. KANTIENGAR..... 538
- Lymphocytic Choriomeningitis as a Systemic Disease. *Edit.*..... 1023

- M**ARCH of Medicine, The—. *Rev.*..... 581
- Meningitis, Meningococcal—; Report of Fifty Cases, Forty Treated with Serum and Ten Treated with Serum and Sulfanilamide. E. P. CAMPBELL 694
- Meningitis, Streptococcal—; Four Cases Treated with Sulfonamides in Which the Etiological Agent Was an Unusual Streptococcus. L. A. RANTZ..... 716
- Meningococcal Meningitis; Report of Fifty Cases, Forty Treated with Serum and Ten Treated with Serum and Sulfanilamide. E. P. CAMPBELL 694
- Meningococcemia, Chronic—Complicated by Acute Endocarditis. R. B. NYE, C. W. SEMISCH and L. MERVES. *Case Rep.*..... 1245
- Menstruation, Liver Function in—. R. HEILIG and N. L. KANTIENGAR.. 538
- Mental Symptoms Following Carbon Disulphide Absorption and Intoxication. F. J. BRACELAND..... 246
- Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. II. Hepatic Dysfunction. J. C. ABELS, P. E. REKERS, G. E. BINKLEY, G. T. PACK and C. P. RHOADS..... 221
- Metabolism, Diseases of—. G. G. DUNCAN, Editor. *Rev.*..... 1256
- Metastatic Processes, The Role of the Vertebral Veins in—. O. V. BATSON 38
- Mononucleosis, Infectious—and Encephalomyelitis. B. L. ZOHMAN and E. G. SILVERMAN. *Case Rep.*..... 1233

- N**AILS, Diseases of the— V. PARDO-CASTELLO. *Rev.*..... 1027
- Nervous Pathways, The Principal— A. T. RASMUSSEN. *Rev.*..... 371
- Nervous System, The Autonomic— J. WHITE and R. SMITHWICK. *Rev.*... 796
- Neuroblastoma (Sympathoblastoma or Neurocytoma) of the Suprarenal Medulla; Report of Three Cases. RALPH M. THOMPSON..... 1206
- Neurocirculatory Asthenia, Anticipation and Diagnosis of— J. T. KING 941
- Neuroses, Treatment of the—by Class Technic. S. B. HADDEN..... 33
- Neutropenia, Primary Splenic—; A Newly Recognized Syndrome, Closely Related to Congenital Hemolytic Icterus and Essential Thrombocytopenic Purpura. B. K. WISEMAN and C. A. DOAN..... 1097
- Non-Icteric Leptospirosis Icterohemorrhagia (Weil's Disease) Contracted while Bathing. P. L. DAVIS and M. S. DAVIS. *Case Rep.*..... 569
- Nutritional Deficiencies; Diagnosis and Treatment. J. B. YOUNG and E. W. PATTON. *Rev.*..... 1256

OBITUARIES:

- Alvarez, John Arthur..... 214
- Austin, Albert E..... 1051
- Burns, Gerald Ross..... 216
- Dailey, M. A..... 217
- Darling, Ira A..... 215
- Finkle, Philip..... 1052
- Fisler, Harry Cattell..... 1051
- Hall, George Washington..... 595
- Helm, Jesse Bundren..... 214
- Hirsch, I. Seth..... 1265
- Lambert, Samuel Waldron, Sr..... 593
- Leech, Frank..... 809
- Marbury, Charles Clagett..... 598
- Morgan, Mark Tad..... 215
- Peters, Leroy S..... 808
- Sleyster, Rock..... 806
- Stoddard, Charles Hatch..... 597
- Weiss, Soma..... 804
- Wolf, Isidore Julius..... 810

- P**AGET'S Disease, Convulsions in—; Electroencephalographic Observations. J. A. MURSON and PAUL CHODOFF..... 762

- Pathological Physiology of the Early Manifestations of Left Ventricular Failure, The— C. S. BURWELL.... 104
- Periarteritis Nodosa; Report of Five Cases. M. M. BANOWITCH, S. H. POLAYES and R. CHARET..... 1149
- Periarteritis Nodosa: with Case Reports. G. M. JONES, JR..... 920
- Pharmacology, Applied— H. A. MCGUIGAN. *Rev.*..... 370
- Physical Diagnosis. W. N. ANDERSON. *Rev.*..... 582
- Physics, Radiologic— C. WEYL, S. R. WARREN, JR. and D. B. O'NEILL. *Rev.*..... 370
- Plasma, The Advantages and Clinical Uses of Desiccated—Prepared by the Adtevac Process. E. E. MUIRHEAD and J. M. HILL..... 286
- Pneumococcic Pneumonia, Antibody Response of Patients with—Treated with Sulfadiazine and Sulfathiazole. M. FINLAND, E. STRAUSS and O. L. PETERSON..... 1
- Pneumococcic Pneumonia, Further Studies on Recurrences in—with Special Reference to the Effect of Specific Treatment. E. STRAUSS and M. FINLAND..... 17
- Pneumococcus Pneumonia Treated with the Sulfonamides, The Relation of Specific Immunity to Recovery from —. *Edit.*..... 577
- Pneumonia, Response to Sulfapyridine in 241 Cases of—, with Especial Reference to Lack of Prompt Response in Some Cases. S. SCHERLIS. 666
- Pneumonias, Chemotherapy of—and Immunity Reactions. J. G. M. BULLOWA, N. H. SHACKMAN and D. STATS..... 57
- Pneumonitis, Eosinophilia and—in Chronic Brucellosis; A Report of Two Cases. K. A. ELSOM and F. J. INGELFINGER..... 995
- Poisoning, The Treatment of Acute Carbon Tetrachloride—with a Report of Two Cases. B. R. ALLISON..... 81
- Potassium Salts in Man, Some Effects of— N. M. KEITH, A. E. OSTERBERG and H. B. BURCHELL..... 879
- Pregnancy, Clinical Roentgenology of —. W. SNOW. *Rev.*..... 796

- Premature Infant, The—; Its Medical and Nursing Care. J. H. HESS and E. C. LUNDEEN. *Rev.*..... 179
- Protamine Zinc and Regular Insulin in Diabetic Patients Followed over a Period of Years, Observations on the Comparable Effects of—. E. P. RALLI, H. BRANDALEONE and H. D. FEIN..... 750
- Protein Derivatives as Factors in Allergy. R. A. COOKE..... 71
- Q**UINIDINE Sulphate, Ventricular Fibrillation in Acute Coronary Artery Thrombosis during the Intravenous Administration of—; Report of a Fatal Case. H. L. RAKOV. *Case Rep.*..... 571
- R**ADIOLOGIC Physics. C. WEYL, S. R. WARREN, JR. and D. B. O'NEILL. *Rev.*..... 370
- Renal Injury, Hypercalcemia and—. *Edit.*..... 176
- Rheumatic Activity in Chronic Rheumatic Heart Disease, The Relationship of Upper Respiratory Infections to—. I. R. JUSTER..... 1137
- Rheumatoid Arthritis, Gold Salts in the Treatment, of—; A Study of 245 Cases. R. L. CECIL, W. H. KAMMERER and F. J. DEPRUME..... 811
- Rickettsial Infections, Vaccination against—. *Edit.*..... 366
- Roentgenology of Pregnancy, Clinical —. W. SNOW. *Rev.*..... 796
- S**AINTE Paul Hospitals, University and—..... 306
- St. Paul: Some of Its Educational, Civic and Religious Institutions..... 625
- Sodium Sulfadiazine, Sulfadiazine and —: A Comparison of Certain of Their Clinical and Pharmacologic Values. C. WHEELER and N. PLUMMER..... 269
- Soldiers, The Minds and Nerves of—. E. L. HANES. *Rev.*..... 180
- Splanchnic Block, Recovery Following —. Anuria Following Hemolytic Reaction to Blood Transfusion;—. H. R. PETERS. *Case Rep.*..... 547
- Splenectomy, Some Indications and Contraindications for—. *Edit.*..... 1253
- Staphylococcal Septicemia, Observations on the Specific Treatment (Type A Antiserum) of—; Second Report. L. A. JULIANELLE..... 303
- Status Dysraphicus and Syringomyelia. B. E. MULVEY and L. A. RIELY.... 966
- Sternal Bone Marrow Puncture, The Clinical Value of—. T. H. MENDELL, D. R. MERANZE and T. MERANZE... 1180
- Stomach Empties Itself, A Theory Concerning the Manner in Which the—. W. T. GIBB, JR..... 94
- Streptococcal Meningitis; Four Cases Treated with Sulfonamides in Which the Etiological Agent Was an Unusual Streptococcus. L. A. RANTZ... 716
- Subacute Bacterial Endocarditis; An Analysis of Fifty Cases with Autopsy Findings. H. C. DENMAN..... 904
- Sulfadiazine and Sodium Sulfadiazine: A Comparison of Certain of Their Clinical and Pharmacologic Values. C. WHEELER and N. PLUMMER..... 269
- Sulfadiazine and Sulfathiazole, Antibody Response of Patients with Pneumococcal Pneumonia Treated with—. M. FINLAND, E. STRAUSS and O. L. PETERSON..... 1
- Sulfadiazine: A Study of Its Effect on Hemolytic Streptococci. C. H. RAMMELKAMP and C. S. KEEFER..... 659
- Sulfanilamide in the Treatment of Erysipelas. L. S. SIEGEL, L. ROSE and A. G. BOWER..... 262
- Sulfanilamide, Report of Fifty Cases, Forty Treated with Serum and Ten Treated with Serum and—. Meningococcal Meningitis;—. E. P. CAMPBELL..... 694
- Sulfapyridine, Report of Two Cases Recovering Following Sulfathiazole and—. *H. Influenzae* Bacteremia;—. C. S. KEEFER and C. H. RAMMELKAMP. *Case Rep.*..... 1221
- Sulfapyridine, Response to—in 241 Cases of Pneumonia, with Especial Reference to Lack of Prompt Response in Some Cases. S. SCHERLIS. 666
- Sulfathiazole, Acute Hemolytic Anemia Caused by—. J. J. BUNIM and M. ISRAEL. *Case Rep.*..... 333
- Sulfathiazole and Sulfapyridine, Report of Two Cases Recovering Following —. *H. Influenzae* Bacteremia;—.

- C. S. KEEFER and C. H. RAMMELKAMP. *Case Rep.*..... 1221
- Sulfathiazole, Antibody Response of Patients with Pneumococcic Pneumonia Treated with Sulfadiazine and —. M. FINLAND, E. STRAUSS and O. L. PETERSON..... 1
- Sulfathiazole Therapy, Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following—; Case Report. I. ROTHSTEIN and S. COHN. *Case Rep.*..... 152
- Sulfonamides and Heparin in the Treatment of Subacute Bacterial Endocarditis. L. WAITZKIN, R. H. SMITH and W. B. MARTIN. *Case Rep.*..... 356
- Sulfonamides, Four Cases Treated with—in Which the Etiological Agent Was an Unusual Streptococcus. Streptococcal Meningitis;—. L. A. RANTZ. 716
- Sulfonamides: Passage into Spinal Fluid and Rectal Absorption. W. C. CUTTING and E. H. SULTAN..... 708
- Sulfonamides, The Relation of Specific Immunity to Recovery from Pneumococcus Pneumonia Treated with the —. *Edit.*..... 577
- Syringomyelia, Status Dysraphicus and —. B. E. MULVEY and L. A. RIELY. 966
- Systolic Murmur, A Pathological Study of the Significance of the—. M. S. REDNICK..... 1197
- T**HROMBOCYTOPENIC Purpura and Carcinoma of Stomach: Report of a Case with Purpura Appearing after Subtotal Gastrectomy. W. H. WILLIS. *Case Rep.*..... 782
- Thrombosis, Ventricular Fibrillation in Acute Coronary Artery—during the Intravenous Administration of Quinidine Sulphate; Report of a Fatal Case. H. L. RAKOV. *Case Rep.*..... 571
- Thyroid Diseases, Exophthalmometric Measurements in Patients with—with Some Discussion of Their Significance. C. GALLI-MAININI..... 415
- Thyroid Gland, Diseases of the—. A. E. HERTZLER. *Rev.*..... 179
- U**LCEr Susceptible Constitution, The Emotional Component of the —. G. DRAPER..... 633
- University and Saint Paul Hospitals... 306
- Uremia, The Concentration of Creatine in Heart, Diaphragm, and Skeletal Muscle in—. H. GROSS and M. SANDBERG..... 737
- Uveoparotitis. M. L. CARNS. *Case Rep.*..... 1239
- Uveoparotitis; A Report of Two Cases. W. HARBIN, JR. and T. S. HARBIN. *Case Rep.*..... 360
- V**ACCINATION against Rickettsial Infections. *Edit.*..... 366
- Ventricular Failure, The Pathological Physiology of the Early Manifestations of Left—. C. S. BURWELL.... 104
- Ventricular Fibrillation in Acute Coronary Artery Thrombosis during the Intravenous Administration of Quinidine Sulphate; Report of a Fatal Case. H. L. RAKOV. *Case Rep.*.... 571
- Vertebral Veins in Metastatic Processes, The Rôle of the—. O. V. BATSON.. 38
- Vitamin D in the Treatment of Infectious Arthritis. C. H. STOCUMB.... 241
- W**ATERHOUSE-FRIDERICHSEN Syndrome, The—: Report of a Case in an Adult. A. T. KWEDAR. *Case Rep.*..... 787
- Whither? J. A. MILLER..... 1003
- Withering, William—: His Contribution to Medicine. J. C. MEAKINS..... 327

